EXHIBIT A

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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ALLERGAN USA, INC. and ALLERGAN INDUSTRIES SAS,	:	CIVIL ACTION
Plaintiffs,	:	
vs.	:	
PROLLENIUM US INC. AND PROLLENIUM MEDICAL TECHNOLOGIES INC.,	:	
Defendants.	:	NO. 20-104-CFC

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Wilmington, Delaware
Wednesday, May 20, 2020
2:32 o'clock, p.m.
***Telephone conference

- - -

BEFORE: HONORABLE COLM F. CONNOLLY, U.S.D.C.J.

- - -

APPEARANCES:

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
BY: JEREMY A. TIGAN, ESQ.

-and-

Valerie J. Gunning
Official Court Reporter

APPEARANCES (Continued):

POLSINELLI PC
BY: GARY E. HOOD, ESQ. and
MARK T. DEMING, ESQ.
(Chicago, Illinois)

Counsel for Plaintiffs

ASHBY & GEDDES
BY: ANDREW C. MAYO, ESQ.

-and-

MEUNIER CARLIN & CURFMAN LLP
BY: JOHN W. HARBIN, ESQ. and
WARREN THOMAS, ESQ.
(Atlanta, Georgia)

Counsel for Defendants

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P R O C E E D I N G S

(The following telephone conference was held beginning at 2:33 p.m.)

THE COURT: Okay. Good afternoon, counsel. Let's start with the plaintiffs first.

MR. TIGAN: Good afternoon, Your Honor. This is Jeremy Tigan with Morris Nichols on behalf of the plaintiffs, and I'm joined by two of my colleagues from Polsinelli today. I have Mark Deming and Gary Hood on the line.

THE COURT: Okay.

MR. DEMING: Good afternoon, Your Honor.

THE COURT: Good afternoon. Let's hear from the defense, please.

MR. MAYO: Good afternoon, Your Honor. This is Andrew Mayo from Ashby & Geddes on behalf of the Prollenium defendants, and I am joined on the telephone today by my co-counsel from Meunier Carlin & Curfman. You have John Harbin and Warren Thomas on the line.

MR. HARBIN: Good afternoon, Your Honor.

THE COURT: All right. Good afternoon.

All right. So I've read the papers. I guess it's the defense's motion, so if you want to start.

MR. MAYO: Your Honor, this is Andrew Mayo. I believe we were scheduled today for a scheduling conference.

THE COURT: Oh, okay. Well, we were, but I've decided I want to address your motion to stay.

MR. MAYO: Okay.

THE COURT: So fair enough. But let's hear. What I'm wondering is why I should schedule the case and I shouldn't just stay this case.

MR. HARBIN: Your Honor, this is John Harbin again for the defendants.

I will be brief because I wasn't anticipating argument, but I will be happy to address it.

We believe --

THE COURT: You don't have to address it. I can just rule. That's fine. Do you want to address it?

MR. HARBIN: We can address it, Your Honor. We think it is a case that definitely warrants a stay.

We have filed, as the papers state, IPRs on all six of the initial patents that were asserted in the initial case and one thing that has changed since we, I think we address it in our reply brief, but one thing that has changed since the initial brief was filed is that we stated in the initial brief that the majority of the claims asserted were at issue.

We're challenging the IPRs, and as the Court is aware, the Patent Trial and Appeal Board has instituted trial on all grounds asserted on all of those six patents.

Now with the plaintiffs' narrowing of the claims, all of the asserted claims in the initial six patents are at issue in the -- are being reviewed in the IPR, and they've, of course, asserted two additional patents.

In the second case, those arise out of the same claimed inventions, same, or very similar specification. The issues will be the same. We expect to file IPRs on those two in the near future on all claims and anticipate, since the rationale would be the same, that the trial will be instituted on those two patents as well. Even if it were not, we believe the claim would be, or the case would be substantially simplified if the IPRs, once the IPRs are decide one way or the other, and we think it would save, you know, the major expenses in the case, fact discovery, Markman hearing, expert reports and testimony, of course, pretrial prep remain to me taken.

So we think judicial economy both for the Court and the parties were certainly be served. We do not think Allergan would be prejudiced at all. Allergan has not sought a preliminary injunction. We are a minor player in this case and Allergan has already entered into a few

licenses of one or more of the patents at issue, so they're not --

THE COURT: So here is one thing. You've got a stay, but it seems to me the argument is much stronger for the first case, not the second case. Why should I stay the second case?

MR. HARBIN: Well, you know, that case even more so, Your Honor. It's just getting going, and there are overlapping issues, but we don't --

THE COURT: You have not filed for review yet. Correct?

MR. HARBIN: Correct, but we will certainly within the next 30 days. Hopefully, before that.

THE COURT: Right. But you --

MR. HARBIN: And we'll have a decision. Sorry, Your Honor. Go ahead.

THE COURT: I was going to say, but you haven't. So you've had some time and you haven't, so I'm just wondering why I should stay that case.

MR. HARBIN: Well, I think, you know, again, Your Honor, I think, you know, it has only been a few months since the case was filed. We will be filing it in the future.

We would be addressing very similar issues as to claims that will be decided in the IPR, so we would lose the

benefit of staying the case, at least partially, if the Court were to stay the existing case and not stay the case that's just getting started.

Again, these --

THE COURT: See, here's my problem.

MR. HARBIN: Go ahead.

THE COURT: My problem is, and I mean it's hard to figure out which of you is, you know, the bad actor in terms of delay. Right? It always is from where you sit in my seat. But if you are saying that the grounds are the same, and they filed their lawsuit when? When did they file the second action? It was in January. Right?

MR. HARBIN: Yes, Your Honor.

THE COURT: So it's five months. You are going to file, you say, the same -- you are going to seek review for the same basis. Why didn't you file right away? It would have made my decision a lot easier. Right? Then I would think you're the good actor here. You are not delaying, but now it's five months and you are telling me you want to stay the second case and you've done nothing. You've not filed it. You say you will file it. Now you're telling me you're going to file it within 30 days and you're basically telling me, yes, but they are one and the same. Why didn't you file it right away?

MR. HARBIN: Your Honor, the multiple -- the

grounds for invalidity are, one of three grounds are the same, but we have multiple claims to deal with in those two patents. I believe it's over -- I don't have the exact number in front of me, but I think it's over 30 claims. We were dealing at the time with over a hundred claims asserted in the initial case, which have only been recently reduce by the plaintiff after some contention.

They just two weeks ago gave us their infringement contentions on the two new patents that are asserted, so under the case law, we did not view this under a lot of Delaware cases as delay, and we also wanted to wait until the initial set of IPRs were decided because that affects -- you know, you're not going to rehash something necessarily if it's decided one way or the other. You may not address it at all.

So we felt like it was more efficient to wait until the IPR decisions came down and we felt like given we have just now gotten the infringement contentions, that this was sufficiently timely in the second case, which again is, you know, just getting started.

THE COURT: Okay. Anything else?

MR. HARBIN: No, Your Honor. Again, I think I was saying we don't believe Allergan will suffer any prejudice, any, you know, any remedy if they are -- you know, if we are found to infringed valid, remedy with money

damages.

They did not seek an injunction. We are a relatively small competitor and they've already shown an inclination to license. They are not averse to other competitors out there.

So that's basically the points. Thank you, Your Honor.

THE COURT: Okay. Thank you. Let's hear from the plaintiff.

MR. HOOD: Thank you, Your Honor. Gary Hood for the plaintiff, Allergan.

We do see this differently. I recognize that there's some attraction to the idea that we put this case on ice and let the PTAB take care of those IPRs, but it's a lot more nuanced than that in this case.

I will start first with the prejudice. There is prejudice here. These are two competitors, Allergan and Prollenium. As I think counsel just acknowledged, Prollenium is selling product, they have been selling product.

The claim is that while they're a minor player, as we understand it, they are selling -- I think the sales are continuing and will continue throughout the period of any stay. And the issue with that and the undue prejudice and on the flip side of that, the benefit to Prollenium by

obtaining a stay and continuing to be able to sell product, infringing product, willfully infringing in our view throughout the course of any stay is not only is that damaging with respect to any kind of patent infringement damages, but what they are also doing is they're taking away market share at this point in this time frame and going forward for any stay from not only Allergan, but those licensees that you just heard about who are paying licensing fees, royalties, to Allergan for sales that are now being taken away, and the concern is that they will continue to be taken away during the course of any stay that this Court might enter.

The concern there is complicated as well, Judge, by the fact that a stay here is not going to be a simple stay for the next nine months or whatever it would be until a final written decision by the Patent Office, which is due in March of next year. The expectation, of course, is, that's not final and binding until the appeal time frame runs. Those appeals right now with the Patent Office to the Federal Court of appeals are taking 15 months.

So we're talking about we're out into June of 2022, two years from now, over two years from now before we have anything along the lines of finality that might be binding on the parties here.

And the other point that counsel mentioned here

that we simply take issue with, Judge. The IPRs may address, and as he put it, simplify some issues that are pending in this case, but it will not simplify a number of issues that are pending that will need to be addressed no matter how those IPRs come out.

Number one, infringement, not addressed at all at the PTAB in any way, shape or form. Invalidity determinations I recognize might influence that. But we simply don't know what is going to happen at the PTAB. Infringement is going to have to be litigated and, in fact, we've been litigating that.

We're looking forward to noninfringement contentions to finally understand from Prollenium why they don't infringe that we expect to get this month based on the proposed joint schedule.

The other issue is the counterclaim that was recently added to the case by Prollenium for inequitable conduct. We intend to aggressively address that, including through motions practice and discovery. That will not be addressed at all or simplified in any way, shape or form by what happens at the PTAB.

So we're look at putting a case on ice based on IPRs that even for the first case to your point, Judge, were not filed for a number of months after we instituted the case despite the fact as we know now from documents that we

have, and this is in our papers, Prollenium has lined up counsel for the IPRs, has lined up an expert. They were ready to go. I don't know why they waited.

And we've been waiting, we've been told for quite awhile now, weeks, if not months, that we're going to see PTAB filings, IPRs on the two patents that we asserted in the second case filed in January, and now we're hearing it's going to be another 30 days.

I don't -- I don't understand why the delay. I do think, and I disagree with counsel that the issues in any IPR filings for those are going to be different because the claims are different in those particular patents, a product by process rather than a composition, but we're talking about some complexities here.

Prollenium has continued to litigate aggressively. We just got done negotiating this joint proposed schedule to get the second case caught up and on the same track to get tried in June of next year with the first case.

We think a stay simply in this case is not the right way to go. Allow the parties to litigate, for that PTAB proceeding to proceed, and to the extent that that somehow is resolved before trial, and I don't think it will, but to the extent there's some clarity there, the parties will take account of that and obviously inform the Court.

But we oppose a stay for those and other reasons stated in our papers.

MR. HARBIN: Your Honor, may I respond to a few of those points?

THE COURT: Yes, but I want you to hold for one second.

(Pause.)

THE COURT: Okay. Go ahead.

MR. HARBIN: Your Honor, a few points. Again, we believe we have moved expeditiously given the schedule of the case.

I would --

THE COURT: So let me ask you about that.

MR. HARBIN: Go ahead.

THE COURT: It's hard with the phone. Excuse me. Sorry.

The thing is, you know what bothers me here is, I already expressed with respect to the second lawsuit what bothers me is, but let me express the concern I have with the first. It's hard to figure out who is the player, you know, that's responsible for delay or whether or not, you know, it's the plaintiff often who, you know, its timing of the filing of the complaint or bringing a subsequent complaint arguably bears responsibility for shaping the calendar.

But, you know, in this case we've got a January 2019 e-mail and your CEO talks about taking action a few days before filing the IPR, but then you don't file it until August. So that's my problem, and that's why, because part of me really wants to stay this case, but it looks to me like you delayed and you played games and that's not fair, and that's why I'm inclined to deny the stay. But if you want to take one more shot, I will listen to you.

MR. HARBIN: Sure, Your Honor. It certainly was no intent to delay or bad faith or gamesmanship and I would like to address the willfulness.

Prollenium is a small company, was very upfront with Allergan. It tried to work it out -- even though it had the view these patents were invalid, it tried to work out a business solution and was very upfront about it. Allergan tried to turn that into saying Prollenium was admitting infringement or acting in bad faith. That's not the case.

And in regard to the IPRs, all they did was state the plan. I mean, Your Honor, it's a lot different to say this is what we're going to and it takes some time to do it.

Number one, we were -- Allergan filed suit on 125 claims across six patents on one accused product, Your Honor, one accused product. It's not like they are dealing

with five, ten, twenty different products with different configurations that Prollenium sells.

They carpet bombed a small company with 125 claims and only agreed to reduce that very recently to 105 claims, still an incredibly unreasonable number and only recently agreed to reduce it to a reasonable number, again now that they're all dealt with and all at risk in the pending IPRs.

So it was not an easy matter putting together effective IPRs on six different patents that have well over 125 claims and we had to choose which ones to focus on and we were hoping to get meaningful infringement contentions from the plaintiff.

Initially, again, we did not get meaningful infringement contentions because they were claiming again 125 and then 105, but we view this as timely and we're trying to do it timely and effectively, but also efficiently, and only address the claims we need to address. And we felt like we were still saving the Court and the parties a lot of expense by doing it, so there was no intent by us to delay.

We were trying -- we were addressing a complex situation and trying to do it effectively. We believe we have again. All grounds have been instituted. All grounds asserted have been instituted.

We agreed and the plaintiff agreed, it makes sense to combine the cases and proceed in one case. It's not a matter of catching up the second case. We're expediting -- we've agreed to expedite the schedule in the second case to be efficient, but there is a lot of work that remains to be done.

They brought up the issue of motions practice on an inequitable conduct counterclaim. Your Honor, we think that's a very well founded counterclaim. We think the Patent Office -- you know, the inventor misrepresented the facts to the Patent Office to get these patents and Magistrate Judge Fallon found that in the initial case, our amended pleading was sufficient to stay the inequitable conduct adequately pleaded and the plaintiff did not object to that finding, so I presume they're talking about a summary judgment motion.

All of that would be avoided by, potentially by staying the cases whereas if we stayed the older cases but somehow don't stay the new case, we're going to be incurring a lot of these expenses anyway.

So to us, again -- and in regard to prejudice, Your Honor, market share, it's a small market that we're selling in, small share. Allergan has not put on any evidence. They've only made attorney argument. They've put on no evidence of actual undue harm that's not compensable

in damages. They put on no evidence of, you know, mandated price reduction or loss of goodwill, anything like that, anything that can't be compensable.

They remain the 900-pound gorilla in this market and they have been very aggressive in dealing with Prollenium. Prollenium is trying to defend itself and trying to invalidate what it believes are invalid patents, and we believe the most efficient way to do that is to stay the case and let these IPRs proceed.

THE COURT: All right. Anything else from the plaintiffs?

MR. HOOD: Your Honor, just briefly. The delay has resulted in hundreds of thousands of dollars certainly from my client litigating this case to get it to a point where we are relatively advanced.

Certainly, the second case was more recently filed, but we had a schedule. As counsel has acknowledged, it's going to get it caught up and enjoined for a trial in a little bit over a year from now. This is not a situation where we've been sitting around doing nothing. It's ready to continue to proceed.

And then one final point, Judge. The IPRs, to the extent they're going to resolve and simplify anything, are going to simplify at best prior art based invalidity, not inequitable conduct, not infringement or any of the

other issues.

This is not a case where with two competitors out there competing in a $500 million-plus a year market, these IPRs are going to resolve this case. Thank you.

THE COURT: Well, let me ask you this. Let me ask you this. Actually, let me ask the defendants this. If I stayed it, would you drop your inequitable conduct counterclaim?

MR. HARBIN: Could we discuss that with our client, Your Honor?

THE COURT: Well, yes.

MR. HARBIN: Can I also respond briefly to the points just made, Your Honor?

THE COURT: Well, no, not yet.

MR. HARBIN: Okay.

THE COURT: Plaintiff, go ahead. So it's not going to get rid of the inequitable conduct, but let's say it did. Okay. Then what?

MR. HOOD: Your Honor, that would resolve the counterclaim for sure, of course, if we were able to reach some kind of an agreement that that went out. Infringement would remain and we still don't have two IPRs filed, I guess they're going to be filed, or an institution decision be done.

THE COURT: Let's be honest. Let me kind of

beat you up the way I beat your --

MR. HOOD: Sure.

THE COURT: -- friend across the aisle.

MR. HOOD: Sure.

THE COURT: I mean, you know, you guys filed a suit in January '19 and then you wait a year and you filed a second lawsuit. You are the big gorilla. This is a smaller company. To my recollection, they have nine percent market share. Is that right?

MR. HOOD: That sounds about right, Judge, based on what I've seen.

THE COURT: All right. And you're making what? 500 million bucks a year off of this product, your products in this market? Is that right?

MR. HOOD: That's correct. Yes. Gross revenue, Judge.

THE COURT: Yes. It sounds to me like you're pretty well positioned to be compensated sufficiently through monetary damages.

Did you bring a preliminary injunction?

MR. HOOD: We did not, Judge.

THE COURT: So I guess you didn't think it was really important to enjoin the sales from the defendant. Right? I mean, you thought you would get compensated by damages when you filed the lawsuit. Right?

MR. HOOD: Well, we certainly hoped so, Judge. A lot of reasons, as I know you know, why a company would not seek preliminary injunctive relief at the start of a suit.

You know, I will say that with respect to this recent suit, these patents were recently issued. This wasn't some intentional holding back of patents to hold back for a later filing, just so the Court knows that.

THE COURT: When were they issued?

MR. HOOD: Your Honor, I don't have those handy. Mark, do you happen to have those? Mr. Deming?

MR. DEMING: Your Honor, I think --

THE COURT: I'm sorry. Did somebody say something?

MR. HOOD: One was in November 2019, Your Honor, and the other one was in August 2019.

THE COURT: All right.

MR. HOOD: November and August.

THE COURT: Okay. I will put you on hold for a second.

(Pause.)

THE COURT: All right, gentlemen. First of all, I appreciate the arguments from counsel, and here's where I am. I just want to ask the plaintiff though, how many claims that are asserted are before the PTAB in the IPRs

that have been instituted?

MR. HOOD: Well, Your Honor, I will count those up real quick. I believe we're down to 56 total, and of those, from the two that are not in the IPR yet --

THE COURT: So you're down to 56 asserted claims is what you are saying?

MR. HARBIN: That's correct, Your Honor, and I believe 20 of those come from the two patents that have not had an IPR petition filed yet.

THE COURT: All right. What do the defendants say to that?

MR. HARBIN: My understanding, Your Honor, is there are 36 asserted claims, not 56, and that 20 are not -- are the in the two newer patents.

MR. THOMAS: Sorry. Your Honor, this is Warren Thomas for defendant Prollenium also.

THE COURT: Yes.

MR. THOMAS: It's 36 patents -- sorry, 36 claims that are asserted are under trial by the PTAB right now. Twenty claims have not been challenged at the PTAB yet. The 20 claims are from the two patents asserted in the 2020 action. The 36 challenged claims, currently challenged claims, are all from the 2019 action.

MR. HOOD: And, Your Honor, Gary Hood for plaintiff.

Yes, I agree with that. That is a better way to put it.

THE COURT: All right. So it's not the 96 that we started with. We're down to where the PTAB has before it 36 claims that are currently asserted in this case. Is that right?

MR. HARBIN: Those are the remaining claims asserted in the initial case. They're all subject to review.

THE COURT: Well, there are 20, but you have not instituted an IPR yet. Right?

MR. HARBIN: Correct. And to be clear, Your Honor, I want to be clear, the PTAB is reviewing a total of 96 claims but only 36 of those are now asserted and existing claims. Then there are 20 more claims that are currently asserted that will be the subject of the new IPRs.

THE COURT: So, in other words, it's fair to say that all of the asserted claims in the first action are before the PTAB. Correct? Do you both agree with that?

MR. HARBIN: Yes, Your Honor.

MR. HOOD: Yes, Your Honor.

THE COURT: Okay.

MR. HARBIN: That is correct, Your Honor.

THE COURT: All right. Yes. Well, for that reason I'm going to stay the first action, the 19-126 action. It will inevitably in my mind and greatly simplify the issues in the case given the fact that all of the claims that are currently asserted in the case are before the PTAB.

You know, prejudice. Is there some prejudice? In all likelihood, yes, but is it undue prejudice given Allergan's size, its market share, the fact that it didn't seek an injunction? I don't think it's unfairly prejudiced. And it's true, the PTAB is not going to address infringement, but it is going to address the validity of all of these claims. So I'm going to stay that case.

I'm going to not stay the second case right now, but if the defendant agrees to forego its inequitable conduct counterclaims and defenses and it files for an IPR, I will entertain at that point and immediately at that point a motion for a stay of the second action.

MR. HARBIN: All right.

THE COURT: All right. Now, it's clear from the comments of counsel, and understandably, I guess, you didn't anticipate that I was going to address the motion to stay at this conference.

Do you want to reconvene and look at the scheduling order you put before me then and put together a

Rule 16 order for the second case?

MR. HOOD: Your Honor, Gary Hood for Allergan.

I think that makes the most sense. We can hopefully address with defense counsel their intentions with respect to the second case and what you just said about the possibility for a stay based on certain conditions.

THE COURT: Okay.

MR. HARBIN: Yes, Your Honor. For the defendants, we agree we should do that for the second case.

THE COURT: Okay. Just one second.

All right. So do you want a deadline to submit something, status report or to submit a Rule 16 order? How do you want to do it? Plaintiff?

MR. HOOD: Yes, Your Honor. Gary Hood for plaintiff.

Yes, I would appreciate that. I think that would help keep us on track with respect to getting something to the Court. I defer to counsel with respect to what he's going to have to do to talk to his client, but I would hope something in the next week to two weeks we would be able to get to the Court.

THE COURT: All right. How about we say two weeks from today? Does that work for the defendant?

MR. HARBIN: Yes, Your Honor.

THE COURT: Okay. All right. Then that's what

we'll do. We will ask, or we'll require that you all submit no later than two weeks from today a proposed scheduling order in the second case or, alternatively, if the defense is willing to forego inequitable conduct counterclaims and unenforceability defenses and it has filed an IPR, I will consider at that point and forthwith a motion to stay the second action. All right?

MR. HOOD: Thank you, Your Honor.

THE COURT: All right. Thank you, all. Take care. Bye-bye.

(Counsel respond, "Thank you, Your Honor.")

(Telephone conference concluded at 3:11 p.m.)

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EXHIBIT B

Paper 1
Filed: June 2, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROLLENIUM US INC.,
Petitioner,

v.

ALLERGAN INDUSTRIE, SAS,
Patent Owner.

Case IPR2020-00901
Patent 10,485,896

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,485,896

TABLE OF CONTENTS

PETITIONER'S EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 10,485,896 to Lebreton (issued Nov. 26, 2019) (the '896 patent or the challenged patent)
1002	Declaration of Dale Devore, Ph.D.
1003	CV of Dale Devore, Ph.D.
1004	Steven Fagien & Arnold W. Klein, *A Brief Overview and History of Temporary Fillers: Evolution, Advantages, and Limitations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 8S–16S (Nov. 2007)
1005	Mary P. Lupo, *Hyaluronic Acid Fillers in Facial Rejuvenation*, Seminars in Cutaneous Medicine and Surgery, Vol. 25, No. 6, 122–126 (Sept. 2006)
1006	Seth L. Matarraso, *Understanding and Using Hyaluronic Acid*, Aesthetic Surgery Journal Vol. 24, No. 4, 361–364 (July/August 2004)
1007	Rhoda S. Narins & Paul H. Bowman, *Injectable Skin Fillers*, Clinics in Plastic Surgery, Vol. 32, Issue 2, 151–162 (April 2005)
1008	Clifford P. Clark III, *Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 27S-32S (Nov. 2007)
1009	Kevin C. Smith, *Practical Use of Juvéderm: Early Experience*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 67S-73S (Nov. 2007)
1010	Rod J. Rohrich, et al., *The Role of Hyaluronic Acid Fillers (Restylane) in Facial Cosmetic Surgery: Review and Technical Considerations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 41S-54S (Nov. 2007)
1011	Michael H. Gold, *Use of Hyaluronic Acid Fillers for the Treatment of the Aging Face*, Clinical Interventions in Aging, Vol. 2, Issue 3, 369-376 (Sept. 2007)
1012	Brian M. Kinney, *Injecting Puragen Plus Into the Nasolabial Folds: Preliminary Observations of FDA Trial*, Aesthetic Surgery Journal, Vol. 26, Issue 6, 741-748 (Nov. 2006), *also available at* https://academic.oup.com/asj/article/26/6/741/238376

Exhibit No.	Description
1013	U.S. Provisional App. Serial No. 61/085,956 (filed Aug. 4, 2008) (priority document for challenged patent)
1014	Gary D. Monheit & Chad L. Prather, *Juvéderm: A Hyaluronic Acid Dermal Filler*, Journal of Drugs in Dermatology, Vol. 6, Issue 11, 1091-1095 (Nov. 2007)
1015	Leslie S. Baumann, et al., *Comparison of Smooth-Gel Hyaluronic Acid Dermal Fillers with Cross-linked Bovine Collagen: A Multicenter, Double-masked, Randomized, Within-Subject Study*, Dermatologic Surgery, Vol. 33 Supplement 2, S128-S135 (Dec. 2007)
1016	Deborah, S. Sarnoff, et al., *Comparison of Filling Agents for Lip Augmentation*, Aesthetic Surgery Journal, Vol. 28, Issue 5, 556-563 (September/October 2008)
1017	Michael S. McCracken, et al., *Hyaluronic Acid Gel (Restylane) Filler for Facial Rhytids: Lessons Learned From American Society of Ophthalmic Plastic and Reconstructive Surgery Member Treatment of 286 Patients*, Ophthalmic Plastic and Reconstructive Surgery, Vol. 22, Issue 3, 188-191 (May-Jun 2006)
1018	Barry L. Eppley & Babak Dadvand, *Injectable Soft-Tissue Fillers: Clinical Overview*, Plastic and Reconstructive Surgery, Vol. 118, Issue 4, 98e-106e (Sept. 15, 2006)
1019	M.J.A. Sapijaszko, *Dermal Fillers: Ever-Expanding Options for Esthetic Use*, Skin Therapy Letter, Vol. 12, No. 8, 4–7 (Oct. 2007)
1020	*Update on Drugs*, Skin Therapy Letter, Vol. 13, No. 3, 8 (Apr. 2008)
1021	Carol A. Toth, et al., *Preclinical evaluation of a novel hyaluronic acid 28 mg/ml lidocaine 0.3% stable combination product*, (abstract), Journal of the American Academy of Dermatology, Vol. 56, No. 2, AB94 (Feb. 2007), Abstract P1039 *and* C. William Hanke, et al., *Effectiveness and durability of a hyaluronic acid 28 mg/ml, lidocaine 0.3% stable combination product as demonstrated in a multicenter, randomized trial* (abstract), Journal of the American Academy of Dermatology, Vol. 56, No. 2, AB94 (Feb. 2007), Abstract P1040

Exhibit No.	Description
1022	Gary D. Monheit, *Hyaluronic Acid Fillers: Hylaform and Captique*, Facial Plastic Surgery Clinics, Vol. 15, No. 1, 77 (Feb. 2007)
1023	Excerpts from file history of U.S. Application 12/393,884 (filed 2/26/2009)
1024	Lebreton Declaration
1025	Yu jia Cui, et al., *The Comparison of Physicochemical Properties of Four Cross-Linked Sodium Hyaluronate Gels with Different Cross-Linking Agents*, Advanced Materials Research, Vols. 396-398, 1506-1512 (2012)
1026	Excerpts from file history of U.S. Application 13/419,079 (filed 3/13/2012)
1027	Claim Construction Order, *Allergan USA, Inc. v. Medicis Aethetics, Inc.*, No. 8:13-cv-01436-AG-JPR, slip op. (Aug. 12, 2014), ECF No. 79, *also available at* 2014 WL 5488895
1028	U.S. Provisional App. Serial No. 61/087,934 (filed Aug. 11, 2008) (priority document for challenged patent)
1029	U.S. Patent Publication No. 2006/0194758 to Lebreton (Lebreton), published Aug. 31, 2006
1030	U.S. Patent Publication No. 2005/0136122 to Sadozai et al. (Sadozai), published June 23, 2005
1031	CTA Product Insert ("Label")
1032	Amy E. Newburger, *Cosmetic Medical Devices and Their FDA Regulation*, Archives of Dermatology, Vol. 142, 225–228 (Feb. 2006)
1033	Excerpts from file history of U.S. Application 12/393,768 (filed 2/26/2009)
1034	*RESERVED*
1035	Inja Bogdan Allemann & Leslie Baumann, *Hyaluronic Acid Gel (Juvedérm) Preparations in the Treatment of Facial Wrinkles and Folds*, Clinical Interventions in Aging, Vol. 3, Issue 4, 629–634 (Dec. 2008)

Exhibit No.	Description
1036	Åke Öhrlund, et al., Extrusion Force and Syringe Dimensions of Two Hyaluronic Acid Dermal Fillers, 8th Anti-aging Medicine World Congress (AMWC) (April 2010)
1037	U.S. Patent Publication No. 2008/0188441 to Reinmuller et al. (Reinmuller 2008), published Aug. 7, 2008, and filed in the U.S. on July 14, 2006
1038	U.S. Patent Publication No. 2005/0142152 to Leshchiner et al., published June 30, 2005
1039	Samuel J. Falcone & Richard A. Berg, *Crosslinked Hyaluronic Acid Dermal Fillers: A Comparison of Rheological Properties*, Journal of Biomedical Materials Research, Vol. 87A, Issue 1, 264–271 (Jan. 15, 2008)
1040	Excerpts from file history of U.S. Application 13/746,170 (filed 1/21/2013)
1041	PCT Application Publication No. WO 2006/002365 A2, published Jan. 5, 2006
1042	U.S. Patent Publication No. 2007/0184087 to Voigts et al., published Aug. 9, 2007 and filed on Jan. 8, 2007
1043	*RESERVED*
1044	U.S. Provisional App. Serial No. 61/096,278 (filed Sept. 11, 2008) (priority document for challenged patent)
1045	Ahmet Tezel & Glenn H. Fredrickson, *The Science of Hyaluronic Acid Dermal Fillers*, Journal of Cosmetic and Laser Therapy, Vol. 10, Issue 1, 35-42 (Mar. 2008)
1046	*Update on Drugs*, Skin Therapy Letter, Vol. 12, No. 7, 8 (Sept. 2007)
1047	U.S. Patent Publication No. 2005/0271729 to Wang, published Dec. 8, 2005
1048	U.S. Patent No. 6,521,223 to Calias et al. (issued Feb. 18, 2003) (Calias)
1049	*RESERVED*
1050	CTA Summary of Safety and Effectiveness, December 20, 2006
1051	December 20, 2007 FDA Letter to Anika Therapeutics, Inc.

Exhibit No.	Description
1052	Prevelle Silk; PMA P030032, February 26, 2008
1053	Mentor Corp. Announces FDA Approval of Prevelle Silk, https://www.businesswire.com/news/home/20080321005064/en/Mentor-Corporation-Announces-FDA-Approval-Prevelle-Silk (Mar. 21, 2008)
1054	Food and Drug Administration, *Medical Devices*; Availability of Safety and Effectiveness Summaries for Premarket Approval Applications, 72 Fed. Reg. 15,885 (Apr. 3, 2007)
1055	*RESERVED*
1056	Robert Stern, et al., *The Many Ways to Cleave Hyaluronan*, Biotechnology Advances, Vol. 25, Issue 6, 537–557 (November/December 2007)
1057	J.W. Kuo, *Practical Aspects of Hyaluronan Based Medical Products*, CRC Press, Taylor & Francis Group, 2006, pp. 34-43, 79-93
1058	U.S. Patent Publication No. 2005/0250939 to Zhao (Zhao), published Nov. 10, 2005
1059	U.S. Patent No. 5,731,298 to Reinmuller (issued Mar. 24, 1998) (Reinmuller 298)
1060–1061	*RESERVED*
1062	U.S. Patent No. 4,605,691 to Balazs et al. (issued Aug. 12, 1986) (Balazs 691)
1063	U.S. Patent No. 4,713,448 to Balazs et al. (issued Dec. 15, 1987) (Balazs 448)
1064	Excerpts from file history of U.S. Application 13/891,052 (filed 5/9/2013)
1065–1081	*RESERVED*
1082	U.S. Patent No. 8,357,795 to Lebreton. (issued Jan. 22, 2013)
1083	*RESERVED*
1084	Joint Claim Construction Chart, Allergan USA, Inc. v. Prollenium US, Inc., No. 1:19-cv-00126 (Jan. 16, 2020), ECF No. 57

Exhibit No.	Description
1085	Allergan Industrie, SAS's September 12, 2019 Response to European Patent Office Opposition Division Preliminary Opinion in proceeding against European Patent 2 323 617 B1, *available at* https://register.epo.org/application?number=EP09785852&lng=en&tab=doclist
1086	Atoosa Maleki et al., *Effect of pH on the Behavior of Hyaluronic Acid in Dilute and Semidilute Aqueous Solutions*, Macromolecular Symposia, Vol. 274, 131-140 (Dec. 29, 2008)
1087	Iuliana Gatej et al., Role of the pH on Hyaluronan Behavior in Aqueous Solution, Biomacromolecules, Vol. 6, Issue 1 (Jan. 2005) (published on web Nov. 6, 2004), *available at* https://pubs.acs.org/doi/10.1021/bm040050m.
1088	Excerpts from file history of U.S. Application 16/186,448 (filed 11/09/2018)
1089	Excerpts from file history of U.S. Application 16/186,451 (filed 11/09/2018)
1090	Y. Tokita & A. Okamoto, *Hydrolytic Degradation of Hyaluronic Acid, Polymer Degradation and Stability*, Vol. 48, Issue 2, 269-273 (1995)

I. INTRODUCTION

Petitioner Prollenium US Inc. (Prollenium) seeks *inter partes* review (IPR) of claims 1-30 of U.S. Patent 10,485,896 (the '896 patent, EX1001), owned by Allergan Industrie, SAS (Allergan or the Patent Owner). This Petition establishes a reasonable likelihood that the prior art renders the challenged claims unpatentable.

Allergan and Prollenium market dermal fillers, which are implantable medical devices that can fill wrinkles or add volume to replace lost tissue. EX1002 ¶ 70. The challenged patent is one of a family of patents directed to "injectable soft tissue fillers and more specifically … hyaluronic acid-based dermal and subdermal fillers including an anesthetic agent," namely lidocaine. EX1001, 1:26-29.

The Board has already instituted seven IPR trials on six patents in the same family. *See, e.g.*, IPR2019-01505, Paper 19 (institution on a "parent" of the challenged patent). As shown in those related proceedings and below, the Office allowed the claims based on an unsubstantiated inventor-declaration of unexpected results that is contradicted by the prior art and testimony of Prollenium's expert. Petitioner therefore requests IPR on this patent and a finding that the claims are unpatentable.

II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing

Prollenium certifies that the challenged patent is available for IPR and that it is not barred or estopped from challenging the claims of the patent on the grounds identified in this Petition.

B. Identification of Challenge and Prior Art

Ground	Basis	Claims	References
1	§ 103(a)	1-7, 9-23, 25-30	Lebreton in view of Sadozai
2	§ 103(a)	8, 24	Lebreton in view of Sadozai and Monheit
3	§ 103(a)	1-7, 9-23, 25-30	Kinney in view of Zhao and Narins
4	§ 103(a)	8, 24	Kinney in view of Zhao, Narins, and Monheit

U.S. Patent Application Pub. No. 2006/0194758 to Lebreton ("Lebreton," EX1029) published August 31, 2006. U.S. Patent Publication No. 2005/0136122 to Sadozai et al. ("Sadozai," EX1030) published June 23, 2005. U.S. Publication 2005/0250939 to Zhao ("Zhao;" EX1058) published on November 10, 2005. These references are prior art under § 102(b).

"Monheit" (EX1022) is an article published in the February 2007 issue of Facial Plastic Surgery Clinics. EX1022 includes a copy of the Table of Contents and Index for that issue of the journal, which are facial indicia of Monheit's publication in February 2007. Monheit is therefore prior art under § 102(b).

"Narins" (EX1007) is a journal article published in the April 2005 issue of the Clinics in Plastic Surgery Journal. EX1007 includes a copy of the Table of Contents and Index for that issue of the journal, which are facial indicia of its publication in April 2005. Narins is therefore prior art under § 102(b).

"Kinney" (EX1012) is an article published in the "November/December 2006" issue of the Aesthetic Surgery Journal. EX1012 includes the journal's cover stamped with date of receipt at the British Library (the U.K. national library) on 25 January 2007, further showing it was publicly available and accessible to interested persons around its publication date. Kinney is therefore prior art under § 102(b).

III. STATE OF THE ART BEFORE THE EARLIEST CLAIMED PRIORITY DATE

A. Background of HA dermal fillers

As a person ages, facial tissue loss and thinning skin contribute to signs of aging. Soft-tissue or dermal "fillers have been developed to help fill in facial lines and depressions and for restoring fat loss-related tissue volume loss. The soft tissue fillers thereby temporarily restore a smoother, more youthful appearance." EX1001, 1:40-44.

A variety of materials have been used in facial dermal fillers, including autologous human fat, animal and human-derived collagen, and synthetic polymers. *See generally* EX1004. By 2008, fillers derived from hyaluronic acid (HA), a polymer composed of repeating β-D-glucuronic acid and N-acetyl-β-D-

glucosamine disaccharide units, were among the most popular in the United States and abroad. See EX1004, 13S-14S; EX1005, 125; EX1002 ¶¶ 72-47.

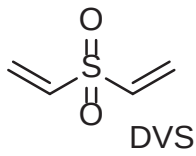
Despite HA's excellent biocompatibility, HA is rapidly degraded by enzymes after injection, so it does not remain in the tissue long enough to function as a filler. To delay the degradation, HA is chemically crosslinked into a water insoluble gel network that prevents enzymes from accessing the polymer. EX1002 ¶¶ 73-74.

No single HA filler is appropriate for every clinical application. EX1002 ¶¶ 75-94 (explaining different applications require different fillers with different characteristics). Consequently, a variety of HA fillers have been developed with different performance characteristics, based on various chemical and physical characteristics of the gel. EX1045, 41; *see also* EX1002 ¶¶ 75-94.

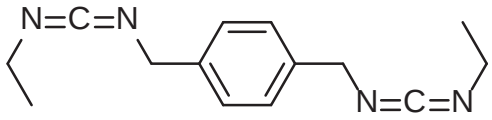
B. Four primary crosslinkers used for dermal fillers

One of the chemical characteristics of a gel is the choice of crosslinker. By 2008, nearly all clinically used crosslinked HA fillers used one of four crosslinkers:

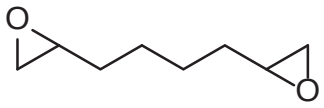
- 1,4-divinylsulfone ("DVS");
- p-phenylene-bis(ethylcarbodiimide) ("PBCDI");
- diepoxyoctane ("DEO"); and
- butanediol diglycidyl ether ("BDDE")



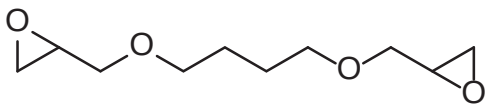
DVS



PBCDI



DEO



BDDE

EX1002 ¶¶ 76-79; *see also* EX1035, 630-631 (describing three of the crosslinkers and indirectly referencing Anika's PBCDI product). Each of these crosslinkers includes two electrophilic functional groups that can react with the primary alcohol and/or carboxylic acid groups in HA. EX1002 ¶ 77.

By August 2008, several crosslinked HA dermal fillers had been approved for sale in the U.S. and abroad, including Hylaform, Captique (HA crosslinked with DVS), Puragen (HA crosslinked with DEO), Restylane and Perlane (HA crosslinked with BDDE), and Juvéderm (another BDDE-crosslinked HA, commercially available from Allergan). EX1002 ¶¶ 95-100. All of these fillers were based on HA crosslinked with one of the four crosslinkers described above.

C. Lidocaine used in crosslinked HA fillers to mitigate pain

Because dermal fillers are administered via injection, injection pain was a common side effect. To reduce pain, many dermal fillers were co-formulated with an anesthetic like lidocaine. E.g., EX1017, 188; EX1002 ¶ 107. Some crosslinked

HA fillers did not contain lidocaine, but physicians sometimes concurrently injected lidocaine to minimize pain. EX1017, 190-191; EX1002 ¶ 108.

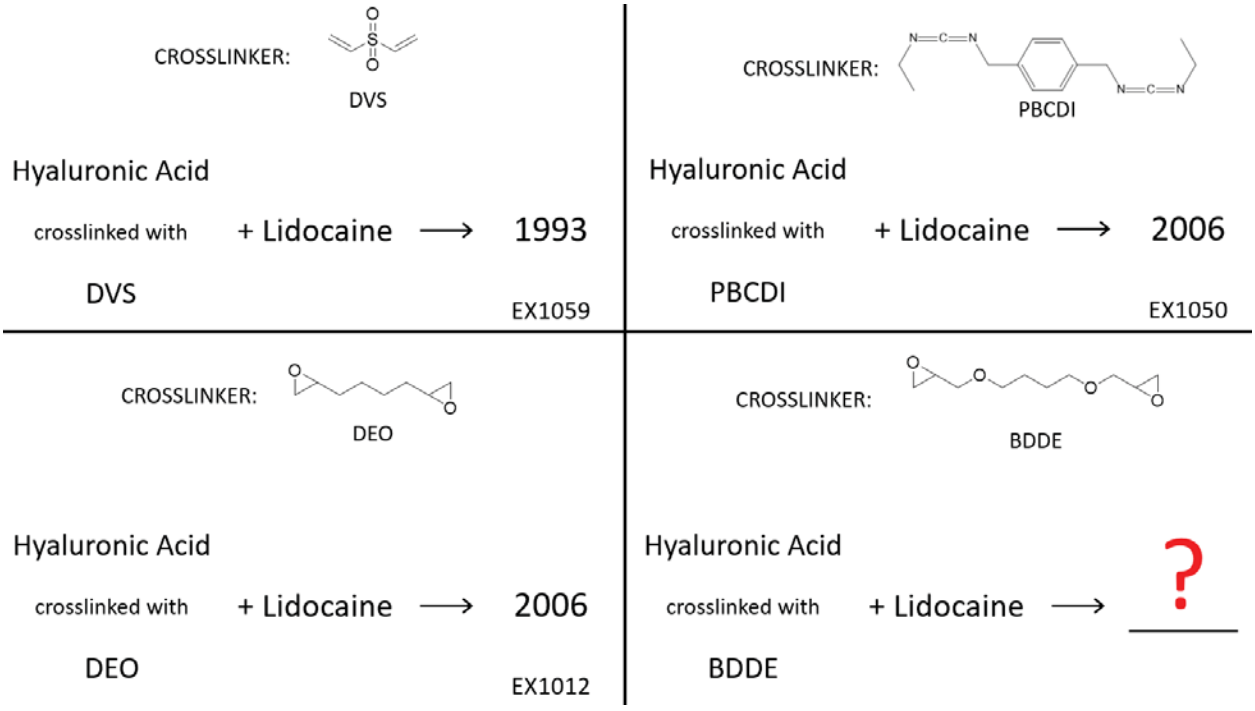
Unsurprisingly, similar efforts were made to incorporate lidocaine *into* crosslinked HA fillers. As early as 1993, lidocaine was incorporated into a product called Hylagel (HA crosslinked with DVS). EX1059, 7:1-17; EX1002 ¶¶ 115-116. This composition was heat sterilized and stored before being injected to treat keloids and scars. EX1059, 7:16-33. Lidocaine was later incorporated into other DVS-crosslinked HA dermal fillers. For example, in spring 2008, FDA approved Prevelle Silk, a DVS-crosslinked HA dermal filler containing 0.3% lidocaine. EX1002 ¶ 112; EX1020, 8 (periodical announcing FDA approval).

Lidocaine had also been incorporated in a PBCDI-crosslinked HA dermal filler. Anika Therapeutics developed a product called Cosmetic Tissue Augmentation Product (CTA), later renamed Elevess, which contained 28 mg/mL PBCDI-crosslinked HA suspended in a buffer solution with 0.3% lidocaine. EX1050, 1; EX1002 ¶¶ 109-110; *see also* EX1054, 15,886 (publishing approval of CTA). CTA was approved for sale by FDA at the end of 2006, but its composition was generally disclosed earlier in a 2005 publication. *See* EX1031, 8 (CTA product label identifying the application number of EX1030); EX1002 ¶ 110.

Lidocaine was also included in a DEO-crosslinked HA dermal filler. A 2006 journal article described the clinical trials and characteristics of “Puragen Plus,”

which included DEO-crosslinked HA and 0.3% lidocaine. EX1012 ("Kinney"), 742; EX1002 ¶¶ 111, 125.

In sum, by early 2007—more than a year before the earliest claimed priority date of the Allergan patents—0.3% lidocaine had successfully been incorporated into compositions containing HA crosslinked with three of the four conventional crosslinking agents: DVS, PBCDI, and DEO.[1]



[1] Other parties were developing BDDE-crosslinked HA fillers including lidocaine around the same time as Allergan. EX1002 ¶ 113.

IV. THE CHALLENGED PATENT

Against this backdrop, Allergan began filing applications generally directed towards crosslinked HA (including BDDE-crosslinked) fillers containing lidocaine, including the one leading to the challenged patent. In August and September 2008, Allergan filed a trio of provisional applications to which the challenged patent claims priority. Despite the prior art and commercially available products described above, the patent contends that it had merely "been proposed to incorporate … lidocaine[] into injectable HA-based compositions," EX1001, 2:30-32, without acknowledging this "proposal" had been successfully implemented into several crosslinked HA fillers.

Either disregarding or unaware of the prior art discussed above, the patent alleges "HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time." EX1001, 2:32-37. However, the patent cites no document supporting this assertion.

A. The Challenged Claims

The '896 patent issued with 30 claims, all of which are challenged in this Petition. Each of the independent claims cover sterile filler compositions

comprising BDDE-crosslinked HA and lidocaine, wherein the compositions are made by certain processes. Claim 1 is representative and recites:

> 1. A dermal filler comprising: [HA] crosslinked with [BDDE], and lidocaine;
>
> wherein the lidocaine is freely released in vivo;
>
> wherein the dermal filler is sterile; and
>
> wherein the dermal filler is made by a process comprising:
>
> crosslinking HA with BDDE to obtain a crosslinked HA composition;
>
> adding lidocaine to the crosslinked HA composition; and
>
> heat sterilizing the crosslinked HA composition with added lidocaine to obtain a sterile dermal filler.

B. The patent was granted based on proffered "unexpected results"

On February 26, 2009, Allergan filed two similar applications claiming priority to the same three provisional applications: Application 12/393,884 (the '884 application), which issued as the '795 patent, and Application 12,393,768 (the '768 application), which issued as the '475 patent. The '896 patent challenged here is related via several continuation applications to the '795 patent. The '884 application included claims directed to, *inter alia,* BDDE-crosslinked HA compositions containing lidocaine. The Examiner relied upon arguments and

evidence submitted by Allergan in the ’884 application when allowing the ’896 patent. Thus, the ’884 application’s prosecution is described here.

In the ’884 application, the Examiner rejected the claims as obvious over prior art that taught BDDE-crosslinked HA dermal fillers in view of other references disclosing the addition of lidocaine to other dermal fillers. Allergan eventually argued, citing a declaration submitted by the inventor, that a POSITA would not have expected a lidocaine-containing HA composition could be sterilized by autoclave. EX1023, 25-28. Specifically, Allergan argued that “it was a surprising and unexpected discovery … that certain [HA] gels … when mixed with lidocaine, could be made to be heat stable and thus useful as dermal fillers.” EX1023, 23. At the time of this response, some pending claims were directed to BDDE-crosslinked HA, while others were directed to HA crosslinked with any crosslinker. EX1023, 18-20 (claims 51-67). Allergan also argued that a POSITA would have expected that autoclave sterilization would unacceptably reduce the composition’s viscosity, thereby making it unsuitable for use as a filler. EX1023, 25.

In support of its arguments, Allergan submitted an Inventor’s Declaration under 37 C.F.R. § 1.132 stating, among other things, that:

- “It was believed that that adding lidocaine to [HA] gel compositions during manufacturing caused degradation of the [HA] prior to injection;”

- "It was not known whether HA compositions comprising lidocaine were stable or not after high temperature sterilization when placed in storage for any significant length of time;" and
- "It was also believed that the instability of HA described above would have caused a viscosity reduction of the HA that would make it unsuitable for soft tissue filling applications."

EX1024 ¶¶ 5, 7-8. The inventor did not identify any references or evidence supporting his characterization of what POSITAs supposedly believed "shortly prior to August 4, 2008." EX1024, ¶ 4.

Allergan also submitted a 2012 article (Cui) purportedly teaching that BDDE-crosslinked HA was less heat stable than HA crosslinked with other crosslinkers. EX1025. According to Allergan, Cui further showed that the autoclave stability of the claimed compositions was unexpected. EX1023, 28. But as explained below (Section VI.F.3, *infra*), none of the crosslinkers tested in the 2012 article were actually in use at the time of the patent's filing.

Allergan also cited Example 4 in the specification, arguing that Samples 1, 2, 3, which were described as "non-cohesive HA gels," "showed a substantial reduction in viscosity" after lidocaine was added and the samples were autoclaved. Allergan claimed this viscosity reduction would have been expected by POSITAs. Allergan contrasted those samples with Samples 4, 5, and 6, described as "cohesive

gels," alleging they "exhibited a much lower, or even insignificant change in viscosity" after adding lidocaine and autoclaving. EX1023, 26-27.

Relying on Allergan's arguments, the Examiner allowed the claims of the '884 application. The Examiner accepted Allergan's characterization of the state of the art and that Example 4 demonstrated unexpected results:

> Applicant argues that one of ordinary skill in the art would have expected degradation of the [HA] gel with addition of lidocaine during sterilization, *as this was what was known in the prior art*. Applicant unexpectedly found that a [HA] gel cross-linked, but not with a non-[HA] biopolymer, mixed with lidocaine and sterilized does not degrade.

EX1023, 9 (emphasis added).

Allergan then filed U.S. 13/419,079 as a continuation of the '884 application. The Examiner, who also examined the parent '884 application, issued an obviousness rejection similar to that in the parent application. Allergan overcame this rejection by arguing it was "believed that crosslinked HA composition when combined with lidocaine were not capable of withstanding high temperature sterilization without a significant reduction in viscosity [which] would make these compositions unsuitable for soft tissue filling applications." EX1026, 18. Allergan resubmitted the Cui reference but did not formally enter the Lebreton declaration into the record. EX1026, 19. The Examiner subsequently allowed the

claims, noting that Allergan "unexpectedly found that a hyaluronic acid gel cross-linked, but not with a non-hyaluronic acid biopolymer, mixed with lidocaine and sterilized does not degrade." EX1026, 9.

After a series of intermediate continuation applications, Allergan eventually filed Application 16/186,448 with the same claims as eventually issued in the '896 patent. Apart from double patenting rejections, which were overcome by terminal disclaimer, the Examiner did not issue any prior art rejections. In the Notice of Allowance, the Examiner cited Allergan's "unexpected results arguments in copending application 12/393768." EX1088, 3.[2]

C. Person of Ordinary Skill in the Art

The POSITA at and before the priority date is a scientist involved in the development of dermal fillers, who would have an advanced degree, such as a Ph.D., M.S., or M.D., and several years of experience developing dermal fillers for cosmetic use, including HA-based dermal fillers. The POSITA would be aware of

[2] As of allowance, the '768 application was not pending; the unexpected results argument had actually been made in the '884 application.

commercially sold dermal fillers, in the United States and abroad, as well as those products for which approvals were being publicly sought. EX1002 ¶¶ 63-66.[3]

V. CLAIM CONSTRUCTION

Claim terms are construed according to their ordinary and customary meaning as understood by a POSITA and the patent's prosecution history. 37 C.F.R. § 42.100(b). Terms not specifically construed below have their ordinary and customary meaning. Petitioner makes the claim construction order from a civil action involving the grandparent '795 patent of record here. See EX1027. Petitioner also provides a Joint Claim Construction Chart reflecting Petitioner and Allergan's *agreed* constructions in a civil action involving six patents in the same family. See EX1084, 4-7. Petitioner's proposed constructions are consistent with those adopted by the district court and agreed-upon by Allergan.

A. *sterile*

In both court proceedings, Allergan agreed *sterile* means a composition that is "substantially free of detectable, viable microorganisms." EX1027, 7; EX1084,

[3] A POSITA would also be aware of the process by which FDA reviews dermal fillers and how FDA publicly communicates the results of such reviews to the public, including by posting the information about the filler on its webpage. EX1002 ¶¶ 67-69; EX1032, 227.

6. This is consistent with the specification of the ’896 patent. *See* EX1001, 5:24-31.

B. *stable*

The *Medicis* court construed *stable* as “maintains at least one of the following aspects: transparent appearance, pH, extrusion force and/or rheological characteristics, [HA] concentration, sterility, osmolarity, and lidocaine concentration.” EX1027, 11. Allergan *agreed* to the same construction in the litigation against Petitioner Prollenium. EX1084, 5. The ’896 patent defines the terms *autoclave stable* and *stable to autoclaving* in the same way. EX1001,5:24-31. The Board should adopt the parties’ agreed construction. Petitioner also contends trial should be instituted under the Board’s “more detailed definition” adopted in prior institution decisions. *See, e.g.*, IPR2019-01508, Paper 19, 13 (citing IPR2017-01906, Paper 15, 9-10 (Mar. 9, 2018)). Allergan’s assent to this proposed construction here was not part of the record in any prior proceeding.

C. *freely released in vivo*

The phrase "freely released in vivo" should have its ordinary meaning.[4] Because the patent does not evaluate the *in vivo* performance of the claimed gels, Petitioner provides a discussion of this limitation.

The only support for the "freely released in vivo" limitation is presented in an *in vitro* assay in Example 5, which is alleged to demonstrate the lidocaine "is freely released from the gels when placed in the skin … and not retained in the gel once implanted." EX1001, 17:26-29 and 60-61. As explained by Dr. DeVore, such *in vitro* assays are frequently used to model expected *in vivo* behavior. EX1002 ¶ 130.

In the Example, a lidocaine-containing gel is placed in water and, after about 48 hours, the lidocaine concentration has equilibrated between the gel and the water. EX1001, 17:24-62; Figure 9. This *in vitro* test is said to be predictive of whether a gel will freely release "once implanted" in the skin—i.e., *in vivo*: "The concentration profile of lidocaine in Sample 5 from Example 4 (FIG. 9) shows that over time it reaches an equilibrium that corresponds to the free release of lidocaine." EX1001, 17:58-60.

[4] In the litigation of the'795 patent, Allergan agreed that "*lidocaine is freely released in vivo*" receives its plain meaning. EX1027, 7-8.

But *in vitro* modeling is not the only way to evaluate the term *freely released in vivo*, as shown by the intrinsic evidence. During the prosecution of the '676 patent, Allegan contrasted the claimed compositions with those that did not *freely release*: "If lidocaine is freely released *in vivo*, a composition cannot provide sustained delivery because it would be released within a few hours rather than over a period of weeks of months." EX1026, 18. Allergan's comments to the Examiner are consistent with the *in vitro* assay. In contrast with the static system of the *in vitro* test in the challenged patents, the environment around a gel actually placed *in vivo* is dynamic, and equilibrium will never be achieved. Instead, as lidocaine diffuses from the gel, it is removed by normal physiological processes, prompting the additional release of lidocaine from the gel according to the laws of thermodynamics. EX1002 ¶¶ 131-132. Thus, the release of lidocaine in an actual *in vivo* system will be faster than the release of lidocaine from the static, *in vitro* system described in the '896 and predecessor patents. EX1002 ¶ 132.

D. *free HA gel*

"Free [HA]" should be construed to mean water soluble HA (i.e., uncrosslinked HA and/or lightly crosslinked HA), just as it was in the prior district court litigation. EX1027, 21. This construction is consistent with the definition and usage in the specification. EX1001, 3:22-25, 5:63-6:4. Thus, the term "free HA gel" in claims 8 and 24 includes gels that contain "very lightly crosslinked" and

"uncrosslinked HA." The '896 patent uses the term "gel" when referring to aqueous compositions containing free HA as well as aqueous compositions containing crosslinked HA. EX1001, 13:51, 14:24-30.

E. *wherein the dermal filler is made be process comprising*

Every claim is in the form of a product-by-process claim, i.e., a product prepared by a certain process. When considering patentability of a product-by-process claim, the focus is on the product—not the process of making it. *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). A process limitation only imparts patentable weight to the claim if the resulting (i.e. claimed) product has "structural and functional differences" that distinguish the claimed product from the prior art. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

1. adjusting the pH of the crosslinked HA composition

Claims 2-5, 17, and 18 include process steps in which the pH of a BDDE-crosslinked HA is adjusted to obtain an alkaline crosslinked HA composition, including adjusting before adding lidocaine in claims 3 & 18 and adjusting to pH above about 7.5 (claim 5) or between about 7.5-8 (claim 4). However, the process

steps should not be afforded any patentable weight because the '896 patent very clearly states that the claimed pH adjustment does not impart functional or structural differences to the fillers.

Example 4 describes comparative experiments in which six crosslinked gels are combined with lidocaine HCl either with pH adjustment (Test 2) or without pH adjustment (Test 1). Although the '896 patent does not describe the particular crosslinkers present in the gels, all three of the provisional applications indicate that Samples 4, 5, and 6 were each Juvéderm products. EX1013, 26; EX1028, 19; EX1044, 30. Each of these products includes HA crosslinked with BDDE. EX1002 ¶ 171; EX1014, 2. The '896 patent states that for at least Samples 5 and 6, no meaningful differences were imparted by the claimed pH adjusting step:

> When Sample 5 was prepared with lidocaine and no pH adjustment, the viscous and elastic properties changed an insubstantial amount (FIG. 6). FIGS. 7 and 8 illustrate that Sample 6 was stable and had similar viscous and elastic properties (G″/G′) when prepared with lidocaine, both with and without pH control.

EX1001, 16:61-17:2. Given Allergan's statement that pH adjustment produced "insubstantial" difference in two of the fillers[5] relative to the same filler which was

[5] Allergan stated that the viscosity of unadjusted Sample 4 did not decrease "to any appreciable extent" compared with pH-adjusted Sample 4. EX1001, 17:9-12.

not pH-adjusted, the claimed process steps cannot be said to impart meaningful functional or structural difference sufficient to give patentable weight to the process steps.

2. homogenizing the crosslinked HA composition before adding lidocaine

While claim 12 is directed to a process where a gel is homogenized before adding lidocaine, the ’896 patent actually describes a different sequence: “*After* the addition of the lidocaine HCl, *or alternatively, during* the addition of the lidocaine HCl, the HA/lidocaine … compositions[] are homogenized ….” EX1001, 11:33-35 (emphasis added); *see also* EX1001, 14:15-22. Thus, as described in the patent, the specifically claimed sequence does not lead to structural or functional differences compared to fillers which are homogenized after or during the addition of lidocaine.

F. *adjusting the pH of the crosslinked HA component to obtain an alkaline crosslinked HA*

The plain meaning of “adjusting” is to “modify” or “alter.” There is no “starting” pH required by any claim, so there is no limitation in which *direction* the pH is adjusted (up or down). The patent includes an Example where the pH of the HA component is *increased* from a “substantially neutral pH” (about 7.2) to between about 7.5 and about 8. EX1001, 14:7-15. But a preference in an example is not a clear and unmistakable disclaimer of processes in which the pH is

decreased. *Cont'l Circuits LLC v. Intel Corp.*, 915 F.3d 788, 797-799 (Fed. Cir. 2019). So, according to the plain meaning of *adjusting*, the claims embrace processes where the HA component has a starting pH that is adjusted *downwards* to some value.

VI. CLAIMS 1-30 ARE UNPATENTABLE

The '896 patent claims sterile dermal fillers containing BDDE-crosslinked HA and lidocaine. Before the relevant filing date, POSITAs had already combined lidocaine with each of the other clinically used crosslinked HA fillers (i.e., DVS, DEO, and PBCDI-crosslinked HA compositions). Adding lidocaine to a BDDE-crosslinked HA filler represented the most natural and obvious next step. The claimed process steps are not afforded any patentable weight, and are obvious over the prior art. As explained in the Grounds below, the purported inventive concept of the '896 patent—the addition of lidocaine to crosslinked HA gels—was made obvious by either of the combinations of primary references Lebreton and Sadozai or Kinney and Zhao.

A. References Relied Upon

1. Lebreton

Lebreton shares the same inventor as the challenged patent and discloses BDDE-crosslinked HA dermal filler compositions. The challenged patent cites Lebreton when explaining how selection of various HA components in dermal

fillers was known to affect characteristics such as extrusion force, elastic modulus, and viscous modulus, among others. EX1001, 9:42-52.

Lebreton discloses dermal fillers obtained by crosslinking a mixture of low and high molecular weight HA starting materials and claims they have improved properties (including "remanence," i.e., stability) relative to prior fillers. EX1029 ¶¶ [0021-0024]. Lebreton teaches that the fillers can be formulated at pH between 6.5-7.5, preferably between 7-7.4, and even more preferably between 7.1-7.3, and that the pH can be controlled using the appropriate buffer solution. EX1029 ¶ [0048].

Lebreton discloses two examples in which a mixture of high and low molecular weight HA is crosslinked with BDDE in 0.25N NaOH. The resulting mixture is neutralized to pH 7.2 using a phosphate buffer and dialyzed. The product is mechanically homogenized, loaded into a syringe, and sterilized in an autoclave. EX1029 ¶¶ [0080-0092].

1. Sadozai

Sadozai discloses PBCDI-crosslinked HA dermal fillers that include lidocaine. EX1030 ¶¶ [0007, 0085]; EX1002 ¶ 122. Sadozai teaches that the dermal fillers may include an anesthetic that can increase the stability of the dermal filler relative to an equivalent filler *without* the anesthetic:

> [T]he storage modulus G' is increased, e.g., the composition is stabilized, by the inclusion of a local anesthetic, e.g., lidocaine,

> compared to a non-stabilized composition, e.g. an identical composition except that the local anesthetic is not included.

EX1030 ¶ [0068].

Sadozai discloses examples in which a dried crosslinked HA is reconstituted in a phosphate buffer containing 0.3% lidocaine hydrochloride (Buffer 4 or 5; Examples 5, 12, 16-18). EX1030 ¶¶ [0084, 0090, 0096-104]; EX1002 ¶ 122. Before reconstitution, several of the samples are sieved to fractionate by particle size. EX1030, ¶ [0096, 0099-0100]. The resulting gels are loaded into a syringe and autoclaved, after which the storage modulus (which relates to viscosity) of the lidocaine-containing crosslinked HA was higher than an otherwise same crosslinked HA without lidocaine. EX1030 ¶¶ [0090, 0107]; EX1002 ¶¶ 122-123 (relating storage modulus to viscosity).

2. Monheit

Monheit details characteristics that can be routinely varied to give fillers the desired physical properties for a particular application, including particle size and ratio of soluble to insoluble HA. EX1022, 78. Monheit specifically notes that free HA can be incorporated in crosslinked HA "as a lubricant for flow characteristics …." EX1022, 78.

3. Kinney

Kinney describes a clinical study comparing two dermal fillers: Restylane, which had been on the market for several years, and Puragen Plus, which was

undergoing FDA clinical trials. EX1012, 741-742. Kinney teaches Restylane is an injectable dermal filler containing 20 mg/mL of BDDE-crosslinked HA particles with a high concentration of "minimally modified HA molecules." EX1012, 741-742. Kinney notes that a "major disadvantage" of existing HA based fillers was the pain that accompanied injection. EX1012, 741.

Kinney also teaches Puragen Plus, a dermal filler containing 20 mg/mL of double-DEO crosslinked HA particles, lidocaine hydrochloride (0.3%), and what a POSITA would recognize as a pH buffer component, which was undergoing clinical trials. EX1012, 742; EX1002 ¶¶ 124-125. Kinney teaches that injection with Puragen Plus caused minimal or no pain for patients. EX1012, 746.

4. Zhao

Zhao describes double-crosslinked HA dermal fillers with improved biostability relative to single-crosslinked HA. *See* EX1058 ¶¶ [0014], [0067]. Zhao describes an example in which double-crosslinked HA was prepared by first crosslinking HA with DEO under alkaline conditions, followed by crosslinking the resultant product with DEO under acidic conditions. EX1058 ¶ [0032]. Zhao teaches that a number of crosslinking agents—including both BDDE and DEO—can be used to prepare double-crosslinked HA using the described methods. EX1058 ¶ [0019-0021].

5. Narins

Narins is a 2005 journal article describing characteristics of several FDA-approved dermal fillers. EX1007, 151, 153. Narins includes a description of the same Restylane product disclosed by Kinney and teaches that Restylane is heat sterilized in its final container and has a shelf life of 1.5 years from date of manufacture. EX1007, 156.

B. Ground 1: Claims 1-7, 9-23, and 25-30 are obvious over Lebreton and Sadozai

Lebreton describes a BDDE-crosslinked HA filler. By August 2008, lidocaine (at 0.3 wt.%) had been incorporated in a range of dermal fillers to mitigate injection pain. EX1002 ¶ 135. Merely adding lidocaine to a prior art filler—which the provisional applications demonstrate is all that Allergan did—is not inventive. *Cf.* EX1013, 16-20 (describing mixing Juvéderm Ultra Plus with lidocaine, adjusting pH to 7.2, and observing the mixture can be autoclave sterilized and that the lidocaine is freely released from the gel).

1. Motivation to Combine

Lebreton discloses BDDE-crosslinked dermal fillers with improved properties over earlier BDDE-crosslinked fillers. The POSITA would have been aware that injection pain was a drawback for these products and would have been motivated to apply the same solution that had been successfully used with other

injectable fillers: adding lidocaine. EX1002 ¶ 135. Sadozai exemplifies such a solution.

As shown in Section III.C above, lidocaine had been successfully incorporated into compositions containing HA crosslinked with the three other conventional crosslinking agents: DVS, PBCDI, and DEO. Two products had already received FDA approval by the patent's earliest filing date. EX1020, 8; EX1052 (Prevelle Silk); EX1019, 5 (Anika's Elevess, an implementation of Sadozai; EX1002 ¶¶ 109, 135-136). A third (Puragen Plus) was approved in Europe and undergoing clinical trials in the U.S. *See* EX1012, 742; EX1002 ¶¶ 111, 135-136. A composition containing BDDE-crosslinked HA and lidocaine was a derivative and predictable next step in view of the success of the other three clinically used crosslinkers. At minimum, adding lidocaine to Lebreton would have been obvious to try.

Moreover, the prior art suggests a reasonable expectation of success that adding lidocaine to Lebreton would produce a lidocaine-containing dermal filler. The repeated successful use of lidocaine across the remaining spectrum of crosslinked HA dermal fillers would have prompted a POSITA to—at minimum—attempt the combination. DVS, PBCDI, and DEO crosslinked HA gels share many more similarities with BDDE-crosslinked gel than differences. EX1002 ¶¶ 77-78, 163, 232. Once crosslinked, all four crosslinkers are devoid of reactive or unstable

functional groups which a POSITA might suspect would unfavorably react in the presence of lidocaine. EX1002 ¶¶ 78, 232-233.

Further, lidocaine had been successfully incorporated into dermal fillers containing more significant chemical differences than the crosslinked-HA fillers discussed above. In the cosmetic field alone, lidocaine had been successfully incorporated into fillers based on synthetic polymers, bovine collagen, and human collagen. EX1002 ¶¶ 107, 136. There is no credible reason why the POSITA would have not expected success in incorporating lidocaine into a BDDE-crosslinked HA too. Even if there had been some uncertainty whether lidocaine could be added to BDDE-crosslinked HA (and there was not), absolute certainty is not necessary for a proposed modification to be obvious. EX1002 ¶¶ 135-136, 140, 145-147. *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1075 (Fed. Cir. 2019) (affirming PTAB's finding of reasonable expectation of success even though the "effect in combination may have been uncertain at the time"); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute"). Nothing in the prior art suggested

any difficulty combining lidocaine with a BDDE-crosslinked gel, such as taught by Lebreton.[6]

The POSITA could have easily adapted the procedure disclosed in Lebreton to incorporate lidocaine into the BDDE-crosslinked gels. In particular, Lebreton teaches that after the crosslinking reaction, the resulting gel is dialyzed with a pH 7.2 phosphate buffer. EX1029 ¶ [0070]. The POSITA could have easily incorporated lidocaine into the buffer solution at a concentration of 0.3% (such as taught by Sadozai), thereby obtaining a BDDE-crosslinked gel containing lidocaine. EX1002 ¶ 136.

The POSITA would have then mechanically homogenized the gel into particles, loaded the composition into a syringe, and sterilized it using an autoclave to arrive at the claimed composition. EX1029 ¶ [0070]; EX1002 ¶¶ 138-140. The resulting composition would meet all the elements of the claims as shown in the detailed analysis below; the claims are obvious.

2. Detailed claim analysis

Independent claim 25 includes many of the common features of the other independent claims, and dependent 26-30 include features that are included in

[6] As noted in Section VI.F.1, below, Allergan's declaration during prosecution proffering "unexpected results" cited no prior art to substantiate the claim.

other challenged claims. Prollenium presents these claims first to illustrate how the prior art teaches those limitations. Other claims are shown obvious by reference (and hyperlinks) to the corresponding limitations in these claims and are obvious for the same reasons.

a. Independent claim 25 and dependent claims 26-30

(i) [25.pre] *A dermal filler product comprising:*
[25.1] *a dermal filler composition comprising*

Lebreton and Sadozai both teach dermal fillers. EX1029 ¶ [0005]; EX1030 ¶¶ [0007, 0012] (HA "effective for tissue augmentation").

(ii) [25.1.1] *an [HA] crosslinked with [BDDE] … wherein the HA is not crosslinked to a non-HA biopolymer*

Lebreton discloses BDDE-crosslinked HA, which is not crosslinked to a non-HA biopolymer. EX1029 ¶¶ [0068-0076]; EX1002 ¶ 137.

(iii) [25.1.2] *between about 0.1% to about 5.0% lidocaine by weight*

Sadozai teaches 0.3% lidocaine. EX1030 ¶ [0107]; EX1002 ¶ 136 (explaining this was a common concentration and effective to mitigate pain).

(iv) [25.1.3] *wherein the composition is sterile* and [25.2] *a syringe containing the sterile composition*

After preparation of the gel, both Lebreton and Sadozai teach loading the gel into syringes and heat-sterilizing in an autoclave. EX1029 ¶ [0070]; EX1030 ¶¶ [0054-0055, 0090]; EX1002 ¶ 138.[7]

(v) [25.3] *wherein the product is made by a process comprising*

While process limitations are not taken into account in an obviousness analysis, the claimed steps are nonetheless obvious. Claim 25 requires the steps of (25.3.1) crosslinking HA with BDDE; (25.3.2) adding lidocaine to the crosslinked product; (25.3.3) packaging said product into a syringe; and (25.3.4) autoclave sterilizing. Lebreton explicitly teaches steps 25.3.1, 25.3.3, and 25.3.4 as shown in elements [25.1.1], [25.1.2], and [25.1.3] above, and the POSITA would have been motivated to add lidocaine to the crosslinked product before packing it into a syringe and autoclaving. The POSITA would have known that once sterilized, no further modifications of the filler should be carried out. EX1002 ¶¶ 138-140.

[7] Notably, Sadozai teaches that lidocaine did *not* decrease filler viscosity after autoclave sterilization. EX1030 ¶ [0107]; EX1002 ¶ 123, 139 (correlating viscosity with storage modulus).

Accordingly, the POSITA would have added lidocaine prior to the sterilization process. EX1002 ¶¶ 138, 140.

(vi) [claim 26] *the syringe has a volume between about 0.8 mL and about 2.5 mL*

Sadozai discloses "loading the gel in a 1 mL glass syringe." EX1030 ¶ [0092].[8] The POSITA could have selected the same syringe to deliver the lidocaine-containing BDDE-crosslinked filler as well. EX1002 ¶ 141.

(vii) [claim 27] *HA concentration of about 20 mg/mL to about 30 mg/mL*

Lebreton discloses a mixture of HA "at a concentration … advantageously of between 20 and 30 mg/g," which is the same concentration claimed. EX1029 ¶ [0049].

(viii) [claim 28] *stable at ambient temperature for at least about 6 months*

"Stable" compositions include those that maintain sterility over a length of time. *See* Section V.A. Lebreton teaches the BDDE-crosslinked gel is sterilized in a syringe. EX1029 ¶ [0070. The POSITA would understand that the product would remain sterile so long as the syringe was not opened, including for at least six months. EX1002 ¶ 143.

[8] The '896 patent disclaims any inventiveness of the recited syringe by admitting that "any syringe known in the art" can be used with its filler. EX1001, 11:49-53.

As explained by Dr. DeVore, the POSITA also would have had a reasonable expectation that the hypothetical composition would also remain shelf-stable like other lidocaine-containing HA dermal fillers known to be approved by FDA and/or undergoing clinical trials by the time of the claimed priority date (including those with lidocaine). See EX1002 ¶¶ 144-147. The POSITA would have expected those other gels would be stable at ambient temperature for at least six months because a company would not undertake a costly clinical trial with a product that would not be competitive in the marketplace. Given that lidocaine-containing fillers based on the PBCDI, DVS, and DEO crosslinkers were all expected to possess the claimed stability, the POSITA would expect a lidocaine containing BDDE-based crosslinker would be stable as well. EX1002 ¶ 144-146. As explained elsewhere in this petition, Allergan did not provide any corroborating evidence supporting its allegation that the POSITA would not have expected a lidocaine-containing HA gel (BDDE-crosslinked or otherwise) could be successfully heat sterilized. EX1002 ¶ 147.

(ix) [claims 29-30] particle size of *greater* or *less* than *"about 200 μm"*

Sadozai teaches the filler product can have an average particle size between about 20 μm and 1,000 μm, and more specifically in the range between 25-250 μm, (EX1030 ¶ [0049]), which is consistent with clinically available filler products. EX1002 ¶ 149-150. The POSITA would have been motivated to explore various

particle size for different filler indications. EX1002 ¶ 149-151. Allergan has not alleged or demonstrated any criticality or unexpected results associated with any of the claimed particle sizes.

b. Independent claim 1 and dependent claims 2-15

(i) Claims 1 and 6

Claim 1 recites many of the same basic features of independent claim 25.

Claim 1	
[1.pre] A dermal filler comprising:	See [25.1][9]
[1.1] [HA] crosslinked with [BDDE], and	See [25.1.1]
[1.2] lidocaine … wherein the lidocaine is freely released in vivo	See [25.1.2] + "freely released" discussion below
[1.3] wherein the dermal filler is sterile; and	See [25.1.3]
[1.4] wherein the dermal filler is made by a process comprising:	See generally [25.3]
[1.4.1] crosslinking HA with BDDE to obtain a crosslinked HA composition;	See [25.3.1]
[1.4.2] adding lidocaine to the crosslinked HA composition; and [claim 6] "adding a solution containing lidocaine HCl."	See [25.3.2] Sadozai teaches the solutions containing lidocaine HCl. EX1030 ¶ [0084]. The POSITA would have used a

[9] Each bracketed limitation or claim reference (such as in this table) is a clickable-hyperlink to the cited discussion in the PDF version of this paper.

Claim 1	
	solution containing lidocaine HCl,[10] as that salt was commonly used when preparing lidocaine-containing dermal fillers. EX1002 ¶ 115, 122, 125; EX1012, 742; EX1059 7:5-10.
[1.4.3] heat sterilizing the crosslinked HA composition with added lidocaine to obtain a sterile dermal filler.	See [25.3.4]

As to the *freely released* portion of element [1.2], the POSITA, understanding that lidocaine was loaded into the crosslinked gel of Sadozai by a diffusion process, would recognize that combining BDDE-crosslinked HA with a lidocaine-containing buffer would load lidocaine into that gel by diffusion as well. EX1002 ¶¶ 154-156. The POSITA would understand that no covalent bonds were formed during the loading process. EX1002 ¶ 156. Although Sadozai includes language suggesting that PBCDI-crosslinked HA may be used for controlled release, the POSITA would not have considered this language relevant to the release of lidocaine. Sadozai is not limited to lidocaine, but instead teaches essentially any drug can be combined with PBCDI-crosslinked, including water

[10] A "solution containing lidocaine" includes solutions containing lidocaine HCl. EX1001, 7:20-21.

insoluble (i.e., fat-soluble EX1030 ¶ [0057]) drugs like steroids. *Id*. In the case of water-insoluble drugs, the drug cannot freely diffuse from the gel *in vivo*, and instead is released as the gel is degraded. EX1030 ¶ [0061]; EX1002 ¶¶ 74, 159 (explaining that only water-soluble drugs, like lidocaine, can freely diffuse in an *in vivo* setting). Moreover, Sadozai compares a 0.3% lidocaine-containing PBCDI-crosslinked dermal filler with Zyderm II, a collagen filler containing 0.3% lidocaine, in a guinea pig assay. EX1030 ¶¶ [0108-0116]. The POSITA would have known that the lidocaine was included in Zyderm II to mitigate pain, and would have reasonably expected that it served the same purpose in the PBCDI-crosslinked gel. EX1002 ¶ 160. The POSITA would have recognized that if lidocaine did not freely diffuse from the gel, it could not function as an anesthetic. EX1002 ¶ 160.

The POSITA's expectation that lidocaine was freely released from the PBCDI-crosslinked gels in Sadozai would have been reinforced by the CTA Summary. The corresponding package insert for CTA cites Sadozai (by Application Serial No.). EX1031, 8. The POSITA would understand that the disclosure in Sadozai was directly related to the product described in CTA Summary, and teaches that over 90% of the lidocaine is eluted within 2 minutes in an *in vitro* assay. EX1002 ¶ 161; EX1050, 6. The POSITA would have expected

similar release characteristics for the lidocaine-containing PBCDI-crosslinked gels taught by Sadozai. EX1002 ¶ 161.

Based on the teachings of Sadozai and CTA Summary, the POSITA would have expected that lidocaine would diffuse from a BDDE-crosslinked gel in a similar fashion to the PBCDI-crosslinked gels. EX1002 ¶¶ 153, 155-156, 161-164. The POSITA would have recognized that there were no functional groups in BDDE-crosslinked HA that would have interacted with lidocaine differently that those present in PBCDI-crosslinked HA. EX1002 ¶¶ 156, 163. As such, the POSITA would have reasonably expected that diffusion would not be inhibited from a BDDE-crosslinked gel. EX1002 ¶ 156. The POSITA would have expected that lidocaine would diffuse from the BDDE-crosslinked gel, both to mitigate pain *in vivo* and to reach equilibrium in an *in vitro* assay like Example 5 of the '676 patent. EX1002 ¶¶ 155-156, 160. In other words, the POSITA would reasonably expect the lidocaine would be "freely released in vivo."

(ii) Claims 2-5: *"adjusting the pH"* process steps

As the claimed process steps do not impart special functional or structural characteristics to the fillers, the process steps do not impart patentability, and claims 2-5 are obvious for the same reasons set forth for claim 1. Nevertheless, the process steps are also obvious.

The POSITA would have been motivated to prepare a composition having the same pre-sterilization pH as the compositions described by Lebreton, e.g., 7.2. EX1029 ¶¶ [0048, 0070, 0076]; EX1002 ¶¶ 177-179. When incorporating lidocaine, the POSITA would have used lidocaine HCl as it was commonly used when preparing lidocaine-containing dermal fillers. EX1002 ¶ 179; EX1030 ¶ [0084]; *see also*, *e.g.*, EX1012, 742; EX1059 7:5-10. The POSITA would have known that lidocaine HCl was weakly acidic, and that adding it directly to Lebreton's gel would lower the pH below the desired 7.2. EX1002 ¶ 179.

With a target pH of 7.2 in mind, the POSITA would have known to account for the reduction in pH caused by introducing acidic lidocaine HCl in the composition. EX1002 ¶ 179. A POSITA would have known that a limited number of simple strategies could be used account for the effect of lidocaine HCl on the pH of the composition so as to arrive at a composition having a target pH of 7.2:

(a) adding lidocaine HCl (thereby lowering the pH below the target pH of 7.2) then adding a base to increase the pH back to the target pH of 7.2;

(b) raising the pH above the target pH of 7.2 and then adding lidocaine HCl to lower the pH to the target pH of 7.2; or

(c) buffering the lidocaine HCl at the target pH of 7.2 and then adding the buffered lidocaine composition to the crosslinked HA composition (such

that the pH remains at the target pH of 7.2 throughout the course of the lidocaine addition).

Sadozai expressly teaches the third option (EX1030 ¶ [0090]), and POSITAs could have easily explored the other two. EX1002 ¶ 179-180. The POSITA knew that HA was stable at the relevant pH levels (EX1002 ¶ 181), and would have reasonably expected that all three options would be successful. As there are only a finite number of possibilities for combining lidocaine HCl with the BDDE-crosslinked composition taught by Lebreton, the POSITA would have been motivated to explore them all.[11] EX1002 ¶¶ 180-181. **Claims 2 and 3** are therefore obvious.

The specific pH levels recited in claims 4 and 5 are the result of routine optimization. The '896 patent indicates that adding lidocaine HCl to a BDDE composition at pH 7.5 to 8 results in a final pH of about 7. EX1001, 14:15-19. Lebreton teaches the fillers are preferably formulated at pH 7-7.4 (EX1029 ¶ [0048]), and the POSITA knew that Restylane was formulated at pH 7. EX1006, 362; EX1002 ¶ 97. The POSITA could have selected either pH = 7 or 7.4 for the lidocaine-containing BDDE-crosslinked fillers as well. The patent states adding

[11] While there are numerous specific processes that could be used, the claims are extremely broad, only requiring a pH adjustment.

0.3% lidocaine to a filler at pH between 7.5-8 results in a final pH of about 7. If the POSITA was targeting a higher pH for the pre-sterilization filler, e.g., 7.4, the POSITA would have been led to a pH adjustment above about 7.5. EX1002 ¶ 182. As such, **claims 4 and 5** are obvious.

(iii) Claims 7 and 9-11: *"passing the crosslinked HA composition through a sieve"* and particle size ranges

For **claim 7**, Sadozai teaches a sieving method that can be used to obtain particles of varying fractions, including particles having average diameter from 125-180 μm, and 180-250 μm. After sieving, the particles are rehydrated in the lidocaine-containing buffer solution. EX1030 ¶ [0052, 0099, 0102]. Instead of purifying the BDDE-crosslinked HA using dialysis (as taught in Lebreton), the POSITA could have instead precipitated the product by alcohol addition, as taught by Sadozai. EX1002 ¶ 183; EX1001, 11:6-8 (admitting both dialysis and alcohol precipitation conventional methods for purifying crosslinked gels). The POSITA could have sieved the crosslinked product, and then reconstituted it using a buffer solution containing lidocaine. EX1002 ¶ 183; EX1030 ¶¶ [0096, 0099].

When sieving the composition, it would have been obvious to select the particle size ranges recited in **claims 9-11**, as shown in [claims 29-30] above. *See also* EX1002 ¶ 183.

(iv) Claim 12: *homogenizing the crosslinked HA composition before adding the lidocaine*

The process step of claim 12 is not entitled to patentable weight, see Sections V.E.2 and VI.B.2.b(ii) above. But even if it did, Lebreton and Sadozai also disclose homogenizing crosslinked compositions. EX1002 ¶ 184; EX1029 ¶¶ [0068-0070]; EX1030 ¶ [0090].

(v) Claims 13-15

Lebreton discloses a mixture of HA "at a concentration … advantageously of between 20 and 30 mg/g," EX1029 ¶ [0049], which is the same concentration in claims 14 and 15. EX1002 ¶ 185. Sadozai teaches 0.3% lidocaine, within the range recited in claim 13 and specified in claim 15. EX1030 ¶ [0107]. See also element [25.1.2] and [claim 27].

c. Independent claim 16 and dependent claims 17-23

Independent claim 16 contains similar limitations as claim 25 (and claim 1) and is obvious for the same reasons, as shown in the table below referring to the argument for corresponding limitations.

Claim 16	
[16.pre] A dermal filler composition comprising:	See [25.1]
[16.1] a composition comprising [HA] crosslinked with [BDDE], wherein the HA is not crosslinked to a non-HA biopolymer, and	See [25.1.1]
[16.2] lidocaine;	See [25.1.2]
[16.3] wherein the dermal filler is made by a process comprising:	See [25.3]

Claim 16	
crosslinking HA with BDDE to obtain a crosslinked HA; adding lidocaine to the crosslinked HA; and heat sterilizing the crosslinked HA with added lidocaine to obtain a sterile dermal filler.	

Claims 17-23	
[Claim 17] wherein the process further comprises adjusting the pH of the crosslinked HA to obtain an alkaline crosslinked HA. [Claim 18] wherein the adjusting the pH is performed before adding the lidocaine.	Same limitations as claims 2 and 3, and obvious for the same reasons. See Section b(ii).
[Claim 19] wherein adding the lidocaine comprises adding a solution containing lidocaine HCl.	See [claim 6]
[Claim 20] wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of at least about 200 μm.	See [claim 29]
[Claim 21] wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of less than about 200 μm.	See [claim 30]
[Claim 22] wherein the dermal filler has a lidocaine concentration of between about 0.1% and about 5.0% w/w.	See [25.1.2]
[Claim 23] wherein the dermal filler has a HA concentration of between about 20 mg/mL and about 30 mg/mL.	See [claim 27]

C. Ground 2: Claims 8 and 24 are obvious over Lebreton, Sadozai, and Monheit

a. Claim 8

In Ground 1, the combination of Lebreton and Sadozai produces a soft tissue filler meeting all the limitations of claim 1. Claim 8 depends from claim 7 and includes the step of adding free HA gel to the filler after it has been passed through the sieve. As described in Monheit, free HA was conventionally included in HA fillers to optimize injection characteristics. EX1002 ¶ 106; EX1022, 78-79; EX1008, 29S; EX1009, 67S. The POSITA would have been motivated to include free HA to optimize the injection characteristics of the filler (EX1002 ¶ 191). Claim 8 covers one sequence of steps (sieve, then add free HA), and there is only one other sequence possible (add free HA, then sieve). The POSITA would have explored both during routine optimization of the manufacturing process. EX1002 ¶ 191.

b. Claim 24

Independent claim 24 contains a combination of limitations the other independent claims, as well as the addition of free HA as in claim 8, though without any recited order. Claim 24 is obvious in Ground 2 as shown in the table below referring to the argument for corresponding limitations. EX1002 ¶ 192.

Claim 24	
[24.pre] A dermal filler composition comprising:	See [25.1]

Claim 24	
[24.1] a [HA] crosslinked with [BDDE], and	See [25.1.1]
[24.2] about 0.3% lidocaine by weight, wherein the lidocaine is freely released in vivo and	See [1.2], Section VI.B.2.b(i)
[24.3] wherein the composition is sterile;	See [25.1.3]
[24.4.1] crosslinking HA with BDDE to obtain a crosslinked HA;	See [25.3]
[24.4.2] adding a free HA gel to the crosslinked HA;	See [claim 8]
[24.4.3] adding a solution of lidocaine HCl to the crosslinked HA; and	See [claim 6]
[24.4.4] autoclaving the crosslinked HA having free HA gel and lidocaine HCl added thereto, to obtain a sterile dermal filler composition.	See [25.3.2]

D. Ground 3: Claims 1-7, 9-23, and 25-30 are obvious over Kinney, Zhao, and Narins

Kinney teaches a double-DEO crosslinked HA filler that includes 0.3 wt.% lidocaine to afford "relatively pain-free injection." EX1012, 742. Kinney states that the double-crosslinking provides advantages including enhanced stability during sterilization, as well as enhanced stability and slower degradation in vivo. EX1012, 742. Zhao teaches double-DEO crosslinked HA, and that BDDE crosslinks are interchangeable with DEO. EX1058 ¶ [0019]. Given the market preference for BDDE-crosslinked HA fillers (EX1002 ¶¶ 195-196), it would have been obvious to simply substitute the DEO crosslinker in Kinney with BDDE (as taught by Zhao) and sterilize the resulting composition using the conventional conditions taught by Narins.

1. Motivation to Combine

Kinney and Narins teach that Restylane, which contained particles of single-BDDE crosslinked HA, was an established dermal filler, but its injections were painful due to lack of lidocaine. EX1012, 741; EX1007, 156. Kinney also discloses Puragen Plus, which included particles of double-DEO crosslinked HA, and that patients preferred it over Restylane because it contained lidocaine. EX1012, 746. The POSITA would have been motivated to exchange the DEO crosslinker in Puragen Plus with a BDDE crosslinker, as BDDE-crosslinked fillers were already established in the marketplace and approved by FDA. EX1002 ¶¶ 195-196.

A POSITA could have easily made particles of double-BDDE crosslinked HA based on the teachings of Zhao. Zhao discloses processes to prepare double crosslinked HA (EX1058 ¶¶ [0083-0093]), including double-BDDE crosslinked HA. EX1058 ¶ [0019]. Because BDDE and DEO are each bis-epoxide crosslinkers, the POSITA would have reasonably expected that Zhao's process could be adapted to use BDDE instead of DEO. EX1002 ¶ 196. As BDDE and DEO are chemically similar, a POSITA would reasonably expect that lidocaine would function analogously in both of the crosslinked gels. EX1002 ¶ 197; *Hoffmann La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014)

("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.").

2. Detailed claim analysis

a. Independent claim 25 and dependent claims 26-30

(i) [25.pre] *A dermal filler product comprising:*
[25.1] *a dermal filler composition comprising*

Kinney, Zhao, and Narins are all directed to dermal fillers. EX1012, 741-742; EX1058 ¶ [0067] (teaching "soft tissue augmentation); EX1007, 156.

(ii) [25.1.1] *[HA] crosslinked with [BDDE] … wherein the HA is not crosslinked to a non-HA biopolymer*

Kinney discloses a BDDE-crosslinked HA filler (Restylane) and a lidocaine-containing, DEO-double crosslinked HA filler (Puragen Plus). EX1012, 741-742. As discussed above, a POSITA would have been motivated to exchange the DEO crosslinker in Puragen Plus with a BDDE crosslinker. EX1002 ¶ 195. The HA in Restylane and Puragen Plus is not crosslinked to a non-HA biopolymer. EX1002 ¶ 200.

(iii) [25.1.2] *between about 0.1% to about 5.0% lidocaine by weight*

"Puragen Plus contains … lidocaine HCl 0.3% …." EX1012, 742; EX1002 ¶ 224 (explaining this was a common concentration and effective to mitigate pain).

(iv) [25.1.3] *wherein the composition is sterile* and [25.2] *a syringe containing the sterile composition*

Kinney discloses Puragen Plus is sterilized and administered by a syringe. EX1012, 742, 748. Narins discloses Restylane is "heat-sterilized in its final container," i.e., a syringe. EX1007, 156; EX1002 ¶ 105. The POSITA would have been motivated to sterilize the double BDDE-crosslinked dermal filler in a syringe that could be sold to clinicians as well. EX1002 ¶¶ 201-202.

(v) [25.3] *wherein the product is made by a process comprising*

While process limitations are not considered in an obviousness analysis, Section V.E, the steps are nonetheless obvious. Claim 25 requires steps of (25.3.1) crosslinking HA with BDDE; (25.3.2) adding lidocaine to the crosslinked product; (25.3.3) packaging said product into a syringe; and (25.3.4) autoclave sterilizing. Double crosslinking HA with BDDE provides step 25.3.1, and the POSITA would have been motivated to add lidocaine to the crosslinked product before packaging it into a syringe and autoclave sterilizing. The POSITA would have known that once sterilized, no further modifications of the filler should be carried out. EX1002 ¶¶ 203-205. Accordingly, the POSITA would have added lidocaine before sterilization. EX1002 ¶ 205.

(vi) [claim 26] *the syringe has a volume between about 0.8 mL and about 2.5 mL*

As noted in Ground 1, the patent admits that "any syringe known in the art" is useful for the claimed filler. EX1001, 11:49-53. As explained by Dr. DeVore, 1 mL syringes were very common in 2008, and used in many commercial fillers. EX1002 ¶ 206. The POSITA could have selected a 1 mL for the double-crosslinked, lidocaine-containing filler as well.

(vii) [claim 27] *HA concentration of about 20 mg/mL to about 30 mg/mL*

Kinney discloses that multiple Restylane formulations "contain a concentration of 20 mg/mL" of HA and that "[e]ach milliliter of Puragen Plus contains 20 mg" of HA. EX1012, 741-742. The POSITA could have selected this concentration for the as-modified composition as well. EX1002 ¶ 207.

(viii) [claim 28] *stable at ambient temperature for at least about 6 months*

"Stable" compositions include those that maintain sterility over a length of time (*See* Section V.A). Given the as-modified composition is sterilized in the final container, *see* Section VI.D.2.a(iv) above, the POSITA would understand that the product would remain sterile for at least the claimed 6 months so long as the final container was not opened. EX1002 ¶¶ 128, 208. Moreover, the POSITA would have reasonably expected that the resulting composition would be shelf-stable for at least the claimed 6 months because all other dermal fillers (including lidocaine-

containing HA fillers) were explicitly taught or expected to have the same stability. The POSITA would expect the same stability for lidocaine-containing, BDDE-double crosslinked compositions. EX1002 ¶¶ 208-210.

(ix) [claims 29-30] particle size of greater or less than *"about 200 μm"*

Both Restylane and Puragen Plus are in the form of particles—the average particle size in Puragen Plus is 220 μm; the average particle size of Restylane is 300-650 μm. EX1012, 741-742. Narins teaches that several different Restylane products were available, differing the particle size and intended tissue application. EX1007, 156-157. The POSITA would have known that particle size affected permanence, hardness, and injectability (EX1002 ¶ 212) and that a desired particle size could be obtained using a sieve method. EX1045, 39; EX1030 ¶ [0096] EX1002 ¶¶ 183, 39. The POSITA could have easily prepared particles falling with the scope of any of claims 29-30 using a sieve based on the intended clinical application. EX1002 ¶ 211-212. Allergan has not alleged or demonstrated any criticality or unexpected results associated with the claimed particle size.

b. Independent claim 1 and dependent claims 2-15

(i) *Claims 1 and 6*

Claim 1 recites many of the same basic features of independent claim 25.

Claim 1	
[1.pre] A dermal filler comprising:	See [25.1]

Claim 1	
[1.1] [HA] crosslinked with [BDDE], and	See [25.1.1]
[1.2] lidocaine … wherein the lidocaine is freely released in vivo	See [25.1.2] + "freely released" discussion below
[1.3] wherein the dermal filler is sterile; and	See [25.1.3]
[1.4] wherein the dermal filler is made by a process comprising:	See generally [25.3]
[1.4.1] crosslinking HA with BDDE to obtain a crosslinked HA composition;	See [25.3.1]
[1.4.2] adding lidocaine to the crosslinked HA composition; and [claim 6] "adding a solution containing lidocaine HCl."	See [25.3.2] Puragen Plus contains lidocaine hydrochloride. EX1012, 742. The POSITA would have used a solution containing lidocaine HCl, which was commonly used when preparing lidocaine-containing dermal fillers. EX1002 ¶ 219; EX1030 ¶ [0084]; EX1059 7:5-10.
[1.4.3] heat sterilizing the crosslinked HA composition with added lidocaine to obtain a sterile dermal filler.	See [25.3.4]

As to the *freely released* portion of element [1.2], Kinney discloses that the inclusion of lidocaine in crosslinked HA filler results in "a relatively pain-free injection." EX1012, 742; *see also* EX1012, 748 ("Injection is minimally painful due to the presence of lidocaine."). The POSITA would have therefore understood

Kinney to teach that the lidocaine in Puragen Plus was "freely released" because it diffused out of the gel quickly enough to produce the pain-minimizing effect upon injection (not hours or days later). *See* EX1002 ¶¶ 215-217; *see also* Section V.C, *supra* (discussing intrinsic evidence of plain meaning of the term).

The POSITA would consequently understand the lidocaine was not covalently bound to the DEO-double crosslinked HA described by Kinney. EX1002 ¶ 215-216 (explaining that a chemical modification to the lidocaine molecule itself would be needed to covalently attach lidocaine to the crosslinked HA, and such a modified compound would no longer be called "lidocaine hydrochloride."). The POSITA would understand that at least a portion (i.e., an effective amount) of lidocaine diffused from Puragen Plus during injection as it was effective to mitigate pain. EX1002 ¶ 216 (explaining that lidocaine cannot exert is biological effect when entrapped within gel). The POSITA would therefore reasonably expect that when Puragen Plus was placed in water, over time the lidocaine concentration would equilibrate between the gel and the water. EX1002 ¶ 217.

The POSITA would understand that there were no functional groups present in BDDE-double crosslinked HA that were not also present in DEO-double crosslinked HA. EX1002 ¶ 77, 217. Accordingly, the POSITA would reasonably expect that lidocaine would diffuse from the BDDE-double crosslinked gel in

similar fashion to a DEO-double crosslinked gel. EX1002 ¶ 217. As such, the POSITA would have reasonably expected that lidocaine would be freely released in vivo from a BDDE-double crosslinked gel.

(ii) Claims 2-5, *"adjusting the pH"* process steps

As discussed in Sections V.E and VI.B.2.b(ii) (Ground 1), the process steps of the claims are not entitled to patentable weight. Nevertheless, the claimed steps are also obvious. The POSITA could have made a BDDE-double crosslinked HA composition according to Zhao. The POSITA would have known the filler should be formulated at a physiologically acceptable pH, for instance 7 as exemplified in Restylane. EX1002 ¶ 220.

As explained in Ground 1, there are a limited number of methods for combining lidocaine hydrochloride with a crosslinked gel buffered to a physiologically pH. See Section B.2.b(ii). The POSITA would have been motivated to explore them all, including methods in which the pH of the double-BDDE crosslinked gel was adjusted to a pH between about 7.5 and 8, as well as above about 7.5 prior to addition of lidocaine hydrochloride. *See also* EX1002 ¶ 182.

(iii) *Claims 7: passing the…composition through a sieve before adding lidocaine*

The POSITA knew that crosslinked HA could be fractionated using a sieve. EX1030 ¶ [0052]; EX1045, 39. Claim 7 covers one sequence of steps (sieve, then add lidocaine), and there is only one other sequence possible (add lidocaine, then

sieve). The POSITA would have explored both during routine optimization of the manufacturing process. EX1002 ¶ 221.

(iv) *Claims 9-11*

The claimed particle sizes are obvious for the reasons explained for claims 29 and 30. The POSITA would have been motivated to prepare particles of various sizes. See [claims 29-30]; EX1002 ¶ 221.

(v) Claim 12: *homogenizing the crosslinked HA composition before adding the lidocaine*

The process step of claim 12 is not entitled to patentable weight, as explained in Ground 1. See Section VI.B.2.b(iv). Nevertheless, the POSITA would have been motivated to homogenize the crosslinked HA to ensure the final filler was uniform both in concentration and injection characteristics. The POSITA could have identified the best stage at which to homogenize the crosslinked HA through routine optimization. EX1002 ¶ 222.

(vi) *Claims 13-15*

These claims are obvious for the reasons explained above for Ground 3, claim element [25.1.2] and [claim 27], namely that Kinney teaches the recited lidocaine and HA concentrations.

c. Independent claim 16 and dependent claims 17-23

Independent claim 16 contains similar limitations as claim 25 (and claim 1) and is obvious for the same reasons, as shown in the table below referring to the argument for corresponding limitations.

Claim 16	
[16.P] A dermal filler composition comprising:	See [25.1]
[16.1] a composition comprising [HA] crosslinked with [BDDE], wherein the HA is not crosslinked to a non-HA biopolymer, and	See [25.1.1]
[16.2] lidocaine;	See [25.1.2]
[16.3] wherein the dermal filler is made by a process comprising: crosslinking HA with BDDE to obtain a crosslinked HA; adding lidocaine to the crosslinked HA; and heat sterilizing the crosslinked HA with added lidocaine to obtain a sterile dermal filler.	See generally [25.3]

Claims 17-23	
[Claim 17] wherein the process further comprises adjusting the pH of the crosslinked HA to obtain an alkaline crosslinked HA. [Claim 18] wherein the adjusting the pH is performed before adding the lidocaine.	Same limitations as claims 2 and 3, and obvious for the same reasons. See Section B.2.b(ii).
[Claim 19] wherein adding the lidocaine comprises adding a solution containing lidocaine HCl.	See [claim 6]
[Claim 20] wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of at least about 200 μm.	See [claim 29]

Claims 17-23	
[Claim 21] wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of less than about 200 μm.	See [claim 30]
[Claim 22] wherein the dermal filler has a lidocaine concentration of between about 0.1% and about 5.0% w/w.	See [25.1.2]
[Claim 23] wherein the dermal filler has a HA concentration of between about 20 mg/mL and about 30 mg/mL.	See [claim 27]

E. Ground 4: Claim 8 and 24 are obvious over Kinney, Zhao, Narins, and Monheit

a. Claim 8

In Ground 3, the combination of Kinney, Zhao, and Narins produces a soft tissue filler meeting all the limitations of claim 1. Claim 8 depends from claim 7 and includes the step of adding free HA to the filler after it has been passed through the sieve. Free (i.e., soluble or uncrosslinked) HA was conventionally included in HA fillers to optimize injection characteristics. EX1002 ¶ 106; EX1022, 78; EX1008, 29S; EX1009, 67S. The POSITA would have been motivated to include free HA to optimize the injection characteristics of the filler and could have done so through routine modification of the Zhao process. EX1002 ¶ 229. Thus, claim 8 is unpatentable as obvious in further view of Monheit.

b. Claim 24

Independent claim 24 contains a combination of limitations the other independent claims, as well as the addition of free HA as in claim 8—though without any recited order other than adding it "to the crosslinked HA." Claim 24 is obvious in Ground 4 as shown in the table below referring to the argument for corresponding limitations. *See also* EX1002 ¶ 230.

Claim 24	
[24.pre] A dermal filler composition comprising:	See [25.1]
[24.1] a [HA] crosslinked with [BDDE], and	See [25.1.1]
[24.2] about 0.3% lidocaine by weight, wherein the lidocaine is freely released in vivo and	See [1.2], Section VI.D.2.b(i)
[24.3] wherein the composition is sterile;	See [25.1.3]
[24.4.1] crosslinking HA with BDDE to obtain a crosslinked HA;	See [25.3]
[24.4.2] adding a free HA gel to the crosslinked HA;	See [25.3.1]
[24.4.3] adding a solution of lidocaine HCl to the crosslinked HA; and	See [claim 8]
[24.4.4] autoclaving the crosslinked HA having free HA gel and lidocaine HCl added thereto, to obtain a sterile dermal filler composition.	See [25.3.2]

F. Allergan cannot rebut the *prima facie* case of obviousness established above

As explained in Section IV.B, the Examiner allowed the claims of the challenged patent (and its related applications) based on Allergan's arguments and proffered evidence pointing to supposed "unexpected results" of the invention. But

the inventor's three-page, unsubstantiated declaration is contradicted by the prior art cited above. Moreover, the 2012 Cui reference does not support Allergan's argument, which the Examiner apparently accepted, that Allergan's BDDE-crosslinked composition was "especially sensitive" to heat sterilization "relative to … non-BDDE crosslinkers." EX1023, 28. Finally, even if evidence of unexpected results was present (it is not), such evidence (or other secondary considerations) must be balanced against the other evidence of obviousness. *E.g.*, *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (holding claims obvious despite agreeing that results were unexpected). Allergan cannot rebut the *prima facie* case of obviousness presented in the Grounds here based on the arguments and evidence presented in prosecution.

1. The uncorroborated Inventor's Declaration does not accurately characterize the state of the art

In the parent '884 application, Allergan made several assertions, based on a § 1.132 Declaration from the inventor, regarding the POSITA's knowledge of the art and the expectations that would be drawn therefrom. Lebreton proffered several assessments of the state of the art, purportedly from the perspective of a POSITA "shortly prior to August 4, 2008":

> It was believed that adding lidocaine to [HA] gel compositions during manufacturing caused degradation of the [HA] prior to injection of the HA as a dermal filler.

> It was believed that lidocaine caused degradation of HA gel compositions during high temperature sterilization.
>
> It was not known whether HA compositions comprising lidocaine were stable or not after high temperature sterilization when placed in storage for any significant length of time.
>
> It was also believed that the instability of HA described above would have caused a viscosity reduction of the HA that would make it unsuitable for soft-tissue filling applications.

EX1024 ¶¶ 5-8. Lebreton's statements were *not* limited to BDDE-crosslinked HA, and Allergan's accompanying Response at the time included pending claims covering use of *any* crosslinker, not just BDDE. EX1023, 18-20 (claims 51-67). Allergan and the inventor cited *no* prior art to support the inventor's opinions. EX1024 ¶¶ 5-8 (repeatedly stating what "was believed"); *see also* EX1023, 25-28.

As shown here, contrary to Lebreton's statements, the totality of the prior art instead gave the POSITA the expectation lidocaine *could* be successfully combined with various crosslinked HA dermal fillers, including a BDDE-crosslinked HA dermal filler. *See* Sections III.C and Grounds, *supra*. The POSITA would have been aware of commercial lidocaine-containing crosslinked HA dermal fillers Elevess, Prevelle Silk and Puragen Plus, as well as the disclosures of the prior art documents cited here, including Sadozai and Kinney. Each of these products and references explicitly state, or at minimum suggest, that crosslinked HA lidocaine-

containing fillers were sterilized, and were sufficiently stable to be approved by FDA as a dermal filler. EX1002 ¶ 241.[12]

There is simply no evidence suggesting that a POSITA would have expected the addition of lidocaine would degrade crosslinked-HA compositions. See EX1002 ¶ 239 (Dr. DeVore unaware of any prior art suggesting issues with addition of lidocaine). In fact, a POSITA would have had the exact *opposite* expectation. Although Puragen Plus and Prevelle Silk are not explicitly described as sterile and stable, the POSITA would have known that these characteristics were necessary for FDA approval. EX1002 ¶ 241. And Sadozai and Kinney disclose that the lidocaine-containing crosslinked HA fillers had viscosities similar to, or even greater than, other crosslinked HA fillers that did not include lidocaine. EX1030 ¶ [0107]; EX1012, 746; *see also* EX1021, AB94 (P1039 poster abstract teaching same). Each of these references supports the conclusion that the POSITA would have reasonably expected that lidocaine could be incorporated into a BDDE-crosslinked HA filler and heat sterilized without compromising the viscosity of the final product. *See* EX1002 ¶ 242. And rather than expecting lidocaine to *degrade*

[12] Abstracts of posters published in the February 2007 issue of the Journal of the American Academy of Dermatology also describe Anika's Elevess/CTA product (an embodiment of Sadozai) as "stable." EX1021, AB94 (P1039-P1040).

HA during autoclave sterilization, the prior art suggested that it could *increase* the stability. *See* EX1002 ¶ 242 (explaining teaching that lidocaine slowed the viscosity reduction process).

There is no evidence to support the inventor's characterization of the prior art. To the contrary, the evidence described herein clearly demonstrates that a POSITA would have reasonably expected that adding lidocaine to a crosslinked HA dermal filler—including the fillers disclosed by Lebreton—would result in a stable dermal filler. The Board should give the Lebreton declaration no weight. *Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003) (affirming Board's reliance on prior publications rather conclusory opinions).

2. Example 4 does not provide evidence of non-obviousness

Lebreton also erroneously asserted the comparative data in the specification supported his conclusions. Lebreton declared that his experiments showed that the Samples 1-3 showed *more* of a decrease in viscosity after autoclave sterilization than Samples 4-5 (the allegedly inventive compositions). EX1024 ¶¶ 13-14. Lebreton declared that it was a "surprising and unexpected discovery" that the HA gels of his application "could be made to be heat and shelf-stable." EX1024 ¶ 15. However, the cited evidence does not establish or suggest meaningful differences between the claimed and the compared compositions.

For unexpected results to be probative of non-obviousness, the claimed subject matter must be compared with the closest prior art, and the difference must not have been expected by the POSITA at the time of the invention. *Kao Corp. v. Unilever U.S., Inc.* 441 F.3d 963, 970 (Fed. Cir. 2006). Moreover, the differences between the claimed invention and prior art must be significant and practical. *Cf. Galderma Labs., L.P. v. Tolmar, Inc.,* 737 F.3d 731, 739 (Fed. Cir. 2013) ("Unexpected results that are probative of non-obviousness are those that are 'different in kind and not merely in degree from the results of the prior art.' Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of [a POSITA]." (citations omitted)). As explained below, the comparative examples in the challenged patent do not represent relevant prior art, nor do they represent a meaningful advance over prior art.

Even if Samples 1-3 experienced a more "substantial" drop in viscosity compared to Samples 4-6, as Allergan argued during prosecution (EX1023, 26), that alone would not make the resulting compositions unsuitable as dermal fillers. As explained by Dr. Devore, the reported viscosities of Samples 1-3 were all within an acceptable range to a POSITA. EX1002 ¶ 251; EX1039, 267. Further, the POSITA would have expected that the sterilized composition would not undergo any further viscosity reduction or other degradation. EX1002 ¶ 252.

Sample 2 is described in the provisional applications as the commercial product "Hylaform," an FDA-approved, DVS-crosslinked HA filler. EX1002 ¶ 253; EX1013, 26. The test results show that when pH control is employed with the lidocaine addition (as a POSITA would have known to do), the viscosity after autoclave remains within an acceptable range for use as a dermal filler. *See* EX1002 ¶ 253. Thus, there is nothing in Example 4 suggesting that Hylaform could not be combined with lidocaine.

The test results and samples do not support patentability or the claimed unexpected results for other reasons as well. For instance, Dr. DeVore explains that the patent's experiments on Sample 1 were irrelevant because he was not aware of such a composition being used as a dermal filler, either in 2008 or now. EX1002 ¶ 249.

As for Sample 3,[13] Allergan argued during prosecution that it lost viscosity to autoclave sterilization. EX1023, 24-28. The data actually shows the opposite and supports that Sample 3 is not indicative of unexpected results. Figure 3 shows that when lidocaine is added to Sample 3 with pH control the resulting composition's

[13] The provisional applications describe this sample as "believed to be similar" to Restylane. EX1013, 26.

viscosity *increases* relative to the non-lidocaine sample after autoclave stabilization by about 10%. See EX1002 ¶ 254; EX1001, Figure 3.

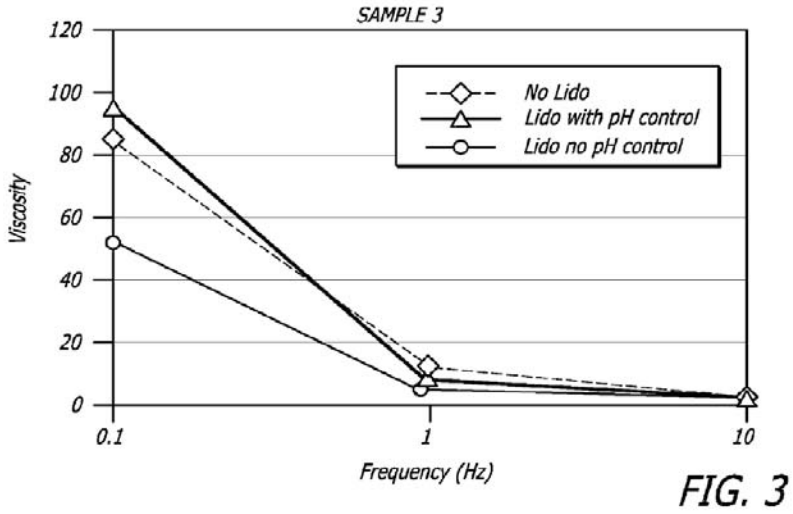


FIG. 3

Allergan acknowledges this fact in the specification of the challenged patent: Sample 3 (a non-cohesive BDDE-crosslinked HA composition) gave the same results as Sample 4 (a cohesive BDDE-crosslinked HA composition). EX1001, 16:55-61. Moreover, it is irrelevant that Samples that were not pH-adjusted exhibited lower viscosities. A POSITA would have understood that a filler should be formulated at a physiologically acceptable pH (e.g., about 7). EX1002 ¶¶ 250, 254. Therefore, examples without pH adjustment would not have impacted a POSITA's expectation that lidocaine could be incorporated in a crosslinked HA dermal filler.

Finally, Allergan also argued that Sample 3 (without pH adjustment) underwent a 35% reduction in viscosity, whereas Sample 4 exhibited a 30%

reduction of viscosity. EX1023, 26-27. As explained by Dr. Devore, these data are irrelevant because such a small difference is meaningless, and a single experiment is not statistically significant. EX1002 ¶ 256.[14]

3. Cui is not relevant

The last piece of "evidence" Allergan relied upon to show "unexpected results" was the Cui reference (EX1025). Allergan argued that Cui "shows" that BDDE-crosslinked HA fillers were "known to be especially sensitive to heat sterilization relative to HA crosslinked with other, i.e. non-BDDE, crosslinkers," so that "the discovery" of Allergan's sterile compositions was "surprising," given the supposedly unstable nature of HA-based gels crosslinked with BDDE even without the addition of lidocaine. EX1023, 28.

Cui compares the stability of BDDE-crosslinked HA with HA crosslinked with three other crosslinking agents. EX1025, 1506. But Cui does *not* test or compare BDDE to *any* of the three crosslinking agents that were known in the art and approved by FDA or undergoing U.S. clinical trials in August 2008. *Compare*

[14] Allergan has not provided any argument or evidence explaining why such a small difference is meaningful to a POSITA. *See Galderma*, 737 F.3d at 739.

id., with Section III.B; EX1002 ¶¶ 244-246.[15] Moreover, none of the crosslinkers appear to have even been used as dermal fillers as of the application's filing date. EX1002 ¶ 245.

Moreover, Cui was published in 2012, well after the claimed priority date of the patent. The reasonable expectation of success is evaluated at the time the invention was made—a later published reference that might have taught away from the claimed invention is irrelevant. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.* 752 F.3d 967, 976 (Fed. Cir. 2014). Cui could not have informed the POSITA's expectation of BDDE-crosslinked HA stability at the time the application was filed.

Thus, Cui is irrelevant to the question of whether Allergan's BDDE-crosslinked HA composition showed unexpected results compared to the other crosslinkers known to POSITAs at the time. EX1002 ¶ 246. Cui is not prior art; but even if it was, Cui is plainly not the "closest prior art" that would be relevant to the obviousness and unexpected results analysis. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

[15] Cui also does not evaluate the effect of lidocaine on any of the compositions it tested. *See generally* EX1025.

4. Other Secondary Considerations

Prollenium is not aware of any other secondary considerations that are sufficient to rebut the *prima facie* case of obviousness presented in the Grounds above.[16] To the extent Allergan should raise secondary indicia such as commercial success, industry praise, or long-felt need, in its Preliminary Response, the Board should institute trial so the parties may develop the evidence before the Board considers the merits of any such argument. *Celltrion, Inc. v. Genetech, Inc.*, IPR2017-01374, Paper 15, 17-18 (Dec. 1, 2017) (instituting trial to permit parties to develop a record regarding secondary considerations first raised in Preliminary Response).

5. Summary

In sum, the evidence cited in this Petition, including both documents and testimony by Dr. DeVore, refute the alleged unexpected results advanced by Allergan during prosecution. In light of the many disclosures of sterilized, non-BDDE-crosslinked HA fillers known to a POSITA at the time, Allergan's "unexpected results" evidence does not hold water; it certainly does not show the

[16] There have been no final determinations regarding secondary indicia in any of the litigations involving the Allergan patents.

claims to be nonobvious. All the evidence cited by Allergan is either incorrect or irrelevant.

The Examiner relied on Allergan's "unexpected results" arguments to allow the claims—in this patent and across its entire family. *See, e.g.*, EX1023, 8-9; EX1033, 8; EX1040, 8; EX1088, 3 (notices of allowance). As shown here, the claims are unpatentable in view of the evidence and the lack of support for Allergan's claim of unexpected results. Finally, these apparent contradictions between the "evidence" that persuaded the Examiner to allow the claims and the new evidence and argument in this Petition are also important to the Board's analysis under § 325(d), as described in the following section. This Petition asks the Board to remedy the Examiner's error, which has propagated throughout an entire family—including applications still pending at the Office.

VII. DISCRETIONARY FACTORS FAVOR INSTITUTION

The factors considered under 35 U.S.C. §§ 314(a) and 325(d) do not weigh in favor of exercising discretion to deny institution. As an initial matter, this is the first Petition challenging this patent. So the *General Plastic* factors and analysis do not apply here. *Cf. Prollenium v. Allergan*, IPR2019-01519, Paper 17, 43-46 (Mar. 19, 2020) (instituting trial, agreeing *General Plastic* does not apply but still finding factors favor Prollenium).

A. Section 325(d) factors

The Board considers several factors to evaluate whether to exercise its discretion under § 325(d). *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 Paper 6, 9-11 (Feb. 13, 2020) (precedential). The Board should not decline to institute trial because even though *one* of the same prior art references was cited by the Office during prosecution, the Grounds here present new evidence and arguments that show how the Office materially erred by relying on the Lebreton Declaration to overcome the rejection.

All references cited in the Grounds except for Zhao appear on the face of the ’896 patent, but the grounds here provide a much more compelling argument for obviousness that was ever assembled by the Office. The Office relied on Lebreton as a primary reference in the ancestor ’884 application, citing Wang and Calias (EX1047, EX1048, respectively) for a motivation to add lidocaine. Allergan overcame Calias rejection by arguing a POSITA would have expected that the addition of lidocaine would unacceptably reduce the composition’s viscosity. EX1023, 23-25. However, Wang and Calias merely *suggest* that lidocaine *could* be added to a HA composition, and do not refute Allergan’s position that lidocaine was expected to degrade the filler upon sterilization. EX1002 ¶ 42.

Here, Kinney and Sadozai cited in the Grounds—as well as CTA Summary, Reinmuller, Toth, and Hanke cited as supporting evidence of the knowledge and skill of a POSITA—all disclose a working embodiment of lidocaine successfully combined with a crosslinked HA composition. The Office plainly overlooked the relevance of each of these references when crediting the inventor's declaration as evidence of obviousness. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 10-11. Allergan never rebutted the Office's prima facie conclusions that the claims were obvious over the prior art; it did not even challenge the Office's assertion that Lebreton taught most of the elements of the claims. Rather, the ancestor patents and the challenged patent were allowed based on Allergan's proffered unexpected results and declaration concerning the supposed state of the art and knowledge of the POSITA. The prior art (and DeVore testimony) cited here contradict the unsupported inventor declaration relied on by the Office. Thus, the Office materially erred in relying on the Lebreton Declaration to overcome the prior art.[17]

[17] The Board reached the same conclusion in declining to exercise its discretion to deny institution in seven proceedings challenging six related patents to this one, relying on the same prior art as the current petition. *E.g.*, IPR2019-01505, Paper 18, 35-42 (Mar. 19, 2020) (finding *Becton Dickinson* factors favored Petitioner and instituting trial).

The asserted grounds here also provide a completely new § 103 analysis based on Kinney and Zhao that was not considered by the Examiner. While the Examiner contended that it would have been obvious to modify the Lebreton reference by adding lidocaine, he apparently did not consider that it would have been equally obvious to modify the crosslinker in the lidocaine-containing filler taught by Kinney, or that Zhao would have enabled the POSITA to do so.

The Board should not exercise its discretion because the substantial evidence cited in this Petition shows the Examiner had an incomplete understanding of the prior art and, consequently, he erred in accepting the applicant's unsubstantiated declaration attesting to "unexpected results." Moreover, this Petition provides evidence showing the inventor's representations about the state of the art at the priority date were incorrect, and the Examiner erred in relying on those representations. Even if the inventor's declaration had accurately characterized the state of the art (it did not), this petition also provides new evidence, not considered by the Office during prosecution, identifying flaws in both the design and interpretation of the comparative experiments. *See* Section VI.F.2. And as explained in Section VI.F and Dr. DeVore's declaration, the Office erred to the extent it relied on Cui as evidence of non-obviousness. Accordingly, the Board should not exercise its discretion under § 325(d) to deny institution.

VIII. CONCLUSION

Challenged claims 1-30 are unpatentable, and Petitioner respectfully requests that the Board institute trial.

IX. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Parties in Interest

The real parties-in-interest are Prollenium US Inc. and Prollenium Medical Technologies Inc.

B. Related Matters

Allergan has asserted the challenged patent and U.S. 10,391,202 (the ’202 patent) against Petitioner Prollenium in *Allergan USA, Inc. et al v. Prollenium US Inc. et al.*, Case-No. 1:20-cv-00104-CFC (D. Del. filed Jan. 23, 2020) (“the 2020 litigation”). Allergan has also asserted six other patents related to the challenged patent in *Allergan USA, Inc. et al v. Prollenium US Inc., et al.*, Case No. 1:19-cv-00126 (D. Del. filed Jan. 22, 2019) (“the 2019 litigation”).

Prollenium has filed petitions challenging all patents asserted in the 2019 Litigation:

- On August 23, 2019, Prollenium filed a petition in IPR2019-01508 challenging related U.S. Patent No. 9,238,013. Trial was instituted on March 19, 2020.
- On September 3, 2019, Prollenium filed petitions IPR2019-01505 and IPR2019-01509 challenging related U.S. Patent Nos. 8,450,475 and

9,358,322, respectively. Trial was instituted on both patents on March 19, 2020.

- On September 16, 2019, Prollenium filed a petition in IPR2019-01617 challenging related U.S. Patent No. 8,822,676. Trial was instituted on March 20, 2020.
- On September 20, 2019, Prollenium filed two petitions, IPR2019-01506 and IPR2019-01632, challenging related U.S. Patent No. 8,357,795. Trial was instituted for both petitions on March 31, 2020.
- On October 25, 2019, Prollenium filed a petition in IPR2020-00084 challenging related U.S. Patent 9,089,519. Trial was instituted on April 10, 2020.

Allergan filed the follow-on, 2020 litigation about three months after the *last* of Prollenium's petitions challenging the patents from the 2019 litigation, after most of Allergan's Preliminary Responses were filed in the first set of IPRs, and even after Prollenium filed its consolidated Reply to Allergan's Preliminary Responses.

On May 20, 2020, the district court granted Prollenium's motion to stay the 2019 litigation pending the outcome of the IPRs listed above. Prollenium is also concurrently filing a petition challenging the '202 patent in proceeding IPR2020-00902. No Scheduling Order has been entered and no trial date has been set in the 2020 litigation as of the filing of this Petition. The parties have conferred with the court about staying the 2020 litigation pending the resolution of this IPR and the

IPR on the ’896 patent, and Prollenium will be filing a motion to stay the 2020 litigation.

Prollenium believes that it would be most efficient to assign all these petitions to the same panel reviewing the other members of Allergan’s patent family. Allergan has multiple issued patents and pending continuations applications claiming priority to one or more of these patents as well.

C. Lead and Back-Up Counsel and Service Information

Petitioner identifies the following counsel for this proceeding:

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Petitioner consents to electronic service by email to:

mcc.prollenium.ipr@mcciplaw.com.

Respectfully submitted,

/Christopher L. Curfman/
Christopher L. Curfman (Reg. No. 52,787)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on June 2, 2020, a copy of this Petition and all exhibits were served on the counsel of record for the Patent Owner by shipping via FedEx Overnight shipping:

Morgan, Lewis & Bockius LLP
600 Anton Boulevard
Suite 1800
Costa Mesa, CA 92626-7653

An electronic copy of the petition and accompanying exhibits has also been served via email on the following counsel representing the Patent Owner in related district court litigation pending IPR proceedings:

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), Petitioner certifies that the foregoing Petition for *Inter Partes* Review contains 13,838 words, excluding the portions as permitted by § 42.24(a).

/Christopher L. Curfman/
Christopher L. Curfman (Reg. No. 52,787)

Paper 1
Filed: June 2, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROLLENIUM US INC.,
Petitioner,

v.

ALLERGAN INDUSTRIE, SAS,
Patent Owner.

Case IPR2020-00902
Patent 10,391,202

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,391,202

TABLE OF CONTENTS

PETITIONER'S EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 10,391,202 to Lebreton (issued August 27, 2019) (the '202 patent or the challenged patent)
1002	Declaration of Dale Devore, Ph.D.
1003	CV of Dale Devore, Ph.D.
1004	Steven Fagien & Arnold W. Klein, *A Brief Overview and History of Temporary Fillers: Evolution, Advantages, and Limitations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 8S–16S (Nov. 2007)
1005	Mary P. Lupo, *Hyaluronic Acid Fillers in Facial Rejuvenation*, Seminars in Cutaneous Medicine and Surgery, Vol. 25, No. 6, 122–126 (Sept. 2006)
1006	Seth L. Matarraso, *Understanding and Using Hyaluronic Acid*, Aesthetic Surgery Journal Vol. 24, No. 4, 361–364 (July/August 2004)
1007	Rhoda S. Narins & Paul H. Bowman, *Injectable Skin Fillers*, Clinics in Plastic Surgery, Vol. 32, Issue 2, 151–162 (April 2005)
1008	Clifford P. Clark III, *Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 27S-32S (Nov. 2007)
1009	Kevin C. Smith, *Practical Use of Juvéderm: Early Experience*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 67S-73S (Nov. 2007)
1010	Rod J. Rohrich, et al., *The Role of Hyaluronic Acid Fillers (Restylane) in Facial Cosmetic Surgery: Review and Technical Considerations*, Plastic and Reconstructive Surgery, Vol. 120 Supplement 6S, 41S-54S (Nov. 2007)
1011	Michael H. Gold, *Use of Hyaluronic Acid Fillers for the Treatment of the Aging Face*, Clinical Interventions in Aging, Vol. 2, Issue 3, 369-376 (Sept. 2007)
1012	Brian M. Kinney, *Injecting Puragen Plus Into the Nasolabial Folds: Preliminary Observations of FDA Trial*, Aesthetic Surgery Journal, Vol. 26, Issue 6, 741-748 (Nov. 2006), *also available at* https://academic.oup.com/asj/article/26/6/741/238376

Exhibit No.	Description
1013	U.S. Provisional App. Serial No. 61/085,956 (filed Aug. 4, 2008) (priority document for challenged patent)
1014	Gary D. Monheit & Chad L. Prather, *Juvéderm: A Hyaluronic Acid Dermal Filler*, Journal of Drugs in Dermatology, Vol. 6, Issue 11, 1091-1095 (Nov. 2007)
1015	Leslie S. Baumann, et al., *Comparison of Smooth-Gel Hyaluronic Acid Dermal Fillers with Cross-linked Bovine Collagen: A Multicenter, Double-masked, Randomized, Within-Subject Study*, Dermatologic Surgery, Vol. 33 Supplement 2, S128-S135 (Dec. 2007)
1016	Deborah, S. Sarnoff, et al., *Comparison of Filling Agents for Lip Augmentation*, Aesthetic Surgery Journal, Vol. 28, Issue 5, 556-563 (September/October 2008)
1017	Michael S. McCracken, et al., *Hyaluronic Acid Gel (Restylane) Filler for Facial Rhytids: Lessons Learned From American Society of Ophthalmic Plastic and Reconstructive Surgery Member Treatment of 286 Patients*, Ophthalmic Plastic and Reconstructive Surgery, Vol. 22, Issue 3, 188-191 (May-Jun 2006)
1018	Barry L. Eppley & Babak Dadvand, *Injectable Soft-Tissue Fillers: Clinical Overview*, Plastic and Reconstructive Surgery, Vol. 118, Issue 4, 98e-106e (Sept. 15, 2006)
1019	M.J.A. Sapijaszko, *Dermal Fillers: Ever-Expanding Options for Esthetic Use*, Skin Therapy Letter, Vol. 12, No. 8, 4–7 (Oct. 2007)
1020	*Update on Drugs*, Skin Therapy Letter, Vol. 13, No. 3, 8 (Apr. 2008)
1021	Carol A. Toth, et al., *Preclinical evaluation of a novel hyaluronic acid 28 mg/ml lidocaine 0.3% stable combination product*, (abstract), Journal of the American Academy of Dermatology, Vol. 56, No. 2, AB94 (Feb. 2007), Abstract P1039 *and* C. William Hanke, et al., *Effectiveness and durability of a hyaluronic acid 28 mg/ml, lidocaine 0.3% stable combination product as demonstrated in a multicenter, randomized trial* (abstract), Journal of the American Academy of Dermatology, Vol. 56, No. 2, AB94 (Feb. 2007), Abstract P1040

Exhibit No.	Description
1022	Gary D. Monheit, *Hyaluronic Acid Fillers: Hylaform and Captique*, Facial Plastic Surgery Clinics, Vol. 15, No. 1, 77 (Feb. 2007)
1023	Excerpts from file history of U.S. Application 12/393,884 (filed 2/26/2009)
1024	Lebreton Declaration
1025	Yu jia Cui, et al., *The Comparison of Physicochemical Properties of Four Cross-Linked Sodium Hyaluronate Gels with Different Cross-Linking Agents*, Advanced Materials Research, Vols. 396-398, 1506-1512 (2012)
1026	Excerpts from file history of U.S. Application 13/419,079 (filed 3/13/2012)
1027	Claim Construction Order, *Allergan USA, Inc. v. Medicis Aethetics, Inc.*, No. 8:13-cv-01436-AG-JPR, slip op. (Aug. 12, 2014), ECF No. 79, *also available at* 2014 WL 5488895
1028	U.S. Provisional App. Serial No. 61/087,934 (filed Aug. 11, 2008) (priority document for challenged patent)
1029	U.S. Patent Publication No. 2006/0194758 to Lebreton (Lebreton), published Aug. 31, 2006
1030	U.S. Patent Publication No. 2005/0136122 to Sadozai et al. (Sadozai), published June 23, 2005
1031	CTA Product Insert (“Label”)
1032	Amy E. Newburger, *Cosmetic Medical Devices and Their FDA Regulation*, Archives of Dermatology, Vol. 142, 225–228 (Feb. 2006)
1033	Excerpts from file history of U.S. Application 12/393,768 (filed 2/26/2009)
1034	*RESERVED*
1035	Inja Bogdan Allemann & Leslie Baumann, *Hyaluronic Acid Gel (Juvedérm) Preparations in the Treatment of Facial Wrinkles and Folds*, Clinical Interventions in Aging, Vol. 3, Issue 4, 629–634 (Dec. 2008)

Exhibit No.	Description
1036	Åke Öhrlund, et al., Extrusion Force and Syringe Dimensions of Two Hyaluronic Acid Dermal Fillers, 8th Anti-aging Medicine World Congress (AMWC) (April 2010)
1037	U.S. Patent Publication No. 2008/0188441 to Reinmuller et al. (Reinmuller 2008), published Aug. 7, 2008, and filed in the U.S. on July 14, 2006
1038	U.S. Patent Publication No. 2005/0142152 to Leshchiner et al., published June 30, 2005
1039	Samuel J. Falcone & Richard A. Berg, *Crosslinked Hyaluronic Acid Dermal Fillers: A Comparison of Rheological Properties*, Journal of Biomedical Materials Research, Vol. 87A, Issue 1, 264–271 (Jan. 15, 2008)
1040	Excerpts from file history of U.S. Application 13/746,170 (filed 1/21/2013)
1041	PCT Application Publication No. WO 2006/002365 A2, published Jan. 5, 2006
1042	U.S. Patent Publication No. 2007/0184087 to Voigts et al., published Aug. 9, 2007 and filed on Jan. 8, 2007
1043	*RESERVED*
1044	U.S. Provisional App. Serial No. 61/096,278 (filed Sept. 11, 2008) (priority document for challenged patent)
1045	Ahmet Tezel & Glenn H. Fredrickson, *The Science of Hyaluronic Acid Dermal Fillers*, Journal of Cosmetic and Laser Therapy, Vol. 10, Issue 1, 35-42 (Mar. 2008)
1046	*Update on Drugs*, Skin Therapy Letter, Vol. 12, No. 7, 8 (Sept. 2007)
1047	U.S. Patent Publication No. 2005/0271729 to Wang, published Dec. 8, 2005
1048	U.S. Patent No. 6,521,223 to Calias et al. (issued Feb. 18, 2003) (Calias)
1049	*RESERVED*
1050	CTA Summary of Safety and Effectiveness, December 20, 2006
1051	December 20, 2007 FDA Letter to Anika Therapeutics, Inc.

Exhibit No.	Description
1052	Prevelle Silk; PMA P030032, February 26, 2008
1053	Mentor Corp. Announces FDA Approval of Prevelle Silk, https://www.businesswire.com/news/home/20080321005064/en/Mentor-Corporation-Announces-FDA-Approval-Prevelle-Silk (Mar. 21, 2008)
1054	Food and Drug Administration, *Medical Devices*; Availability of Safety and Effectiveness Summaries for Premarket Approval Applications, 72 Fed. Reg. 15,885 (Apr. 3, 2007)
1055	*RESERVED*
1056	Robert Stern, et al., *The Many Ways to Cleave Hyaluronan*, Biotechnology Advances, Vol. 25, Issue 6, 537–557 (November/December 2007)
1057	J.W. Kuo, *Practical Aspects of Hyaluronan Based Medical Products*, CRC Press, Taylor & Francis Group, 2006, pp. 34-43, 79-93
1058	U.S. Patent Publication No. 2005/0250939 to Zhao (Zhao), published Nov. 10, 2005
1059	U.S. Patent No. 5,731,298 to Reinmuller (issued Mar. 24, 1998) (Reinmuller 298)
1060–1061	*RESERVED*
1062	U.S. Patent No. 4,605,691 to Balazs et al. (issued Aug. 12, 1986) (Balazs 691)
1063	U.S. Patent No. 4,713,448 to Balazs et al. (issued Dec. 15, 1987) (Balazs 448)
1064	Excerpts from file history of U.S. Application 13/891,052 (filed 5/9/2013)
1065–1081	*RESERVED*
1082	U.S. Patent No. 8,357,795 to Lebreton. (issued Jan. 22, 2013)
1083	*RESERVED*
1084	Joint Claim Construction Chart, Allergan USA, Inc. v. Prollenium US, Inc., No. 1:19-cv-00126 (Jan. 16, 2020), ECF No. 57

Exhibit No.	Description
1085	Allergan Industrie, SAS's September 12, 2019 Response to European Patent Office Opposition Division Preliminary Opinion in proceeding against European Patent 2 323 617 B1, *available at* https://register.epo.org/application?number=EP09785852&lng=en&tab=doclist
1086	Atoosa Maleki et al., *Effect of pH on the Behavior of Hyaluronic Acid in Dilute and Semidilute Aqueous Solutions*, Macromolecular Symposia, Vol. 274, 131-140 (Dec. 29, 2008)
1087	Iuliana Gatej et al., Role of the pH on Hyaluronan Behavior in Aqueous Solution, Biomacromolecules, Vol. 6, Issue 1 (Jan. 2005) (published on web Nov. 6, 2004), *available at* https://pubs.acs.org/doi/10.1021/bm040050m.
1088	Excerpts from file history of U.S. Application 16/186,448 (filed 11/09/2018)
1089	Excerpts from file history of U.S. Application 16/186,451 (filed 11/09/2018)
1090	Y. Tokita & A. Okamoto, *Hydrolytic Degradation of Hyaluronic Acid, Polymer Degradation and Stability*, Vol. 48, Issue 2, 269-273 (1995)

I. INTRODUCTION

Petitioner Prollenium US Inc. (Prollenium) seeks *inter partes* review (IPR) of claims 1-30 of U.S. Patent 10,391,202 (the ’202 patent, EX1001), owned by Allergan Industrie, SAS (Allergan or the Patent Owner). This Petition establishes a reasonable likelihood that the prior art renders the challenged claims unpatentable.

Allergan and Prollenium market dermal fillers, which are implantable medical devices that can fill wrinkles or add volume to replace lost tissue. EX1002 ¶ 75. The challenged patent is one of a family of patents directed to “injectable soft tissue fillers and more specifically … hyaluronic acid-based dermal and subdermal fillers including an anesthetic agent,” namely lidocaine. EX1001, 1:22-25.

The Board has already instituted seven IPR trials on six patents in the same family. *See, e.g.*, IPR2019-01505, Paper 19 (institution on a “parent” of the challenged patent). As shown in those related proceedings and below, the Office allowed the claims based on an unsubstantiated inventor-declaration of unexpected results that is contradicted by the prior art and testimony of Prollenium’s expert. Petitioner therefore requests IPR on this patent and a finding that the claims are unpatentable.

II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing

Prollenium certifies that the challenged patent is available for IPR and that it is not barred or estopped from challenging the claims of the patent on the grounds identified in this Petition.

B. Identification of Challenge and Prior Art

Ground	Basis	Claims	References
1	§ 103(a)	1-25, 27-30	Lebreton in view of Sadozai and Clark
2	§ 103(a)	26	Lebreton in view of Sadozai and Smith
3	§ 103(a)	1-25, 27-30	Kinney in view of Zhao and Clark
4	§ 103(a)	26	Kinney in view of Zhao and Smith

U.S. Patent Application Pub. No. 2006/0194758 to Lebreton ("Lebreton," EX1029) published August 31, 2006. U.S. Patent Publication No. 2005/0136122 to Sadozai et al. ("Sadozai," EX1030) published June 23, 2005. U.S. Publication 2005/0250939 to Zhao ("Zhao;" EX1058) published on November 10, 2005. These references are prior art under § 102(b).

"Kinney" (EX1012) is an article published in the "November/December 2006" issue of the Aesthetic Surgery Journal. EX1012 includes the journal's cover stamped with date of receipt at the British Library (the U.K. national library) on 25

January 2007, further showing it was publicly available and accessible to interested persons around its publication date. Kinney is therefore prior art under § 102(b).

"Clark" (EX1008) and "Smith" (EX1009) are articles published in the November 2007 Supplement of the Journal Plastic and Reconstructive Surgery. These references qualify as prior art under at least § 102(a)[1] and are relied upon to indicate the level of skill and motivations in the art, corroborate expert testimony about the state of the art, and disclose characteristics of prior art products known long before the earliest claimed priority date. *Yeda Research v. Mylan Pharm. Inc*., 906 F.3d 1031, 1041 (Fed. Cir. 2018) (affirming Board's use of "non-prior art" document to show knowledge and motivations of a POSITA regarding prior art)); *In re Koller*, 613 F.2d 819, 824, n.5 (C.C.P.A. 1980).

III. STATE OF THE ART BEFORE THE EARLIEST CLAIMED PRIORITY DATE

A. Background of HA dermal fillers

Soft-tissue or dermal "fillers have been developed to fill in facial lines and depressions and [restore] … tissue volume loss," which are signs of aging, and

[1] For purposes of identifying the prior art qualification, Petitioner assumes that the priority date of the claims is August 4, 2008 (the earliest claimed priority date), without conceding that any claim of the patent is entitled to that priority date.

they "temporarily restore a smoother, more youthful appearance." EX1001, 1:36-40.

A variety of materials have been used in facial dermal fillers, including autologous human fat, animal and human-derived collagen, and synthetic polymers. EX1004. By 2008, fillers derived from hyaluronic acid (HA), a polymer composed of repeating β-D-glucuronic acid and N-acetyl-β-D-glucosamine disaccharide units, were among the most popular in the United States and abroad. *See* EX1004, 13S-14S; EX1005, 125; EX1002 ¶¶ 80.

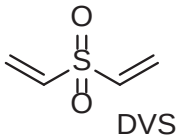
Despite HA's excellent biocompatibility, it is rapidly degraded by enzymes after injection, so it does not remain in the tissue long enough to function as a filler. To delay the degradation, HA is chemically crosslinked into a water insoluble gel network that prevents enzymes from accessing the polymer. EX1002 ¶ 82.

No single HA filler is appropriate for every application. EX1002 ¶ 83 (explaining different applications require different fillers with different characteristics). A variety of HA fillers have been developed with different performance characteristics, based on various chemical and physical characteristics of the gel. EX1045, 41; EX1002 ¶¶ 83-102.

B. Four primary crosslinkers used for dermal fillers

One of the chemical characteristics of a gel is the choice of crosslinker. By 2008, nearly all clinically used crosslinked HA fillers used one of four crosslinkers:

- 1,4- divinylsulfone ("DVS");
- p-phenylene-bis(ethylcarbodiimide) ("PBCDI");
- diepoxyoctane ("DEO"); and
- butanediol diglycidyl ether ("BDDE")



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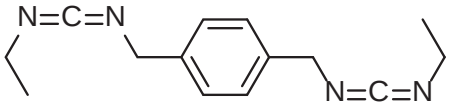

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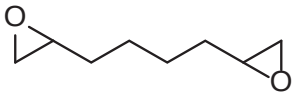
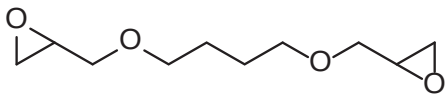


DEO



BDDE

EX1002 ¶ 85; EX1035, 630-631 (describing three of the crosslinkers and indirectly referencing Anika's PBCDI product). Each of these crosslinkers includes two electrophilic functional groups that can react with the primary alcohol and/or carboxylic acid groups in HA. EX1002 ¶ 85.

By August 2008, several crosslinked HA dermal fillers had been approved for sale in the U.S. and abroad, including Hylaform, Captique (HA crosslinked with DVS), Puragen (HA crosslinked with DEO), Restylane and Perlane (HA crosslinked with BDDE), and Juvéderm (another BDDE-crosslinked HA, commercially available from Allergan). EX1002 ¶¶ 103-108. All of these fillers were based on HA crosslinked with one of the four crosslinkers described above.

C. Lidocaine used in crosslinked HA fillers to mitigate pain

Because dermal fillers are administered via injection, injection pain was a common side effect. To reduce pain, many dermal fillers were co-formulated with an anesthetic like lidocaine. E.g., EX1017, 188; EX1002 ¶ 117. Some crosslinked HA fillers did not contain lidocaine, but physicians sometimes concurrently injected lidocaine to minimize pain. EX1017, 190-191; EX1002 ¶ 118.

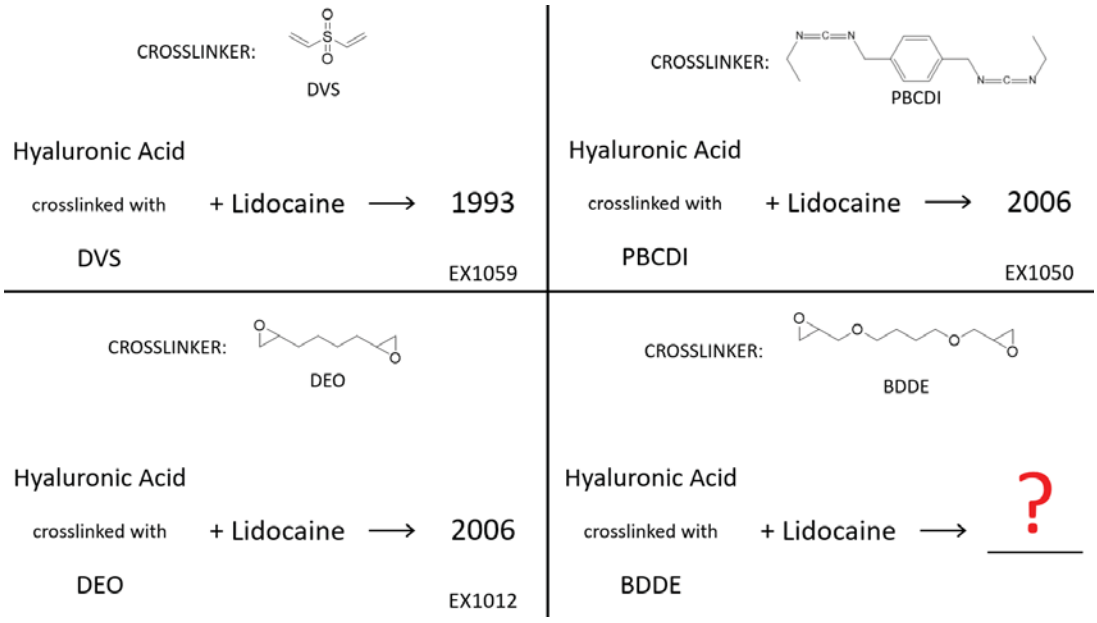
Unsurprisingly, similar efforts were made to incorporate lidocaine *into* crosslinked HA fillers. As early as 1993, lidocaine was incorporated into a product called Hylagel (HA crosslinked with DVS). EX1059, 7:1-17 ("Reinmuller"); EX1002 ¶¶ 125-127. This composition was heat sterilized and stored before being injected to treat keloids and scars. EX1059, 5:30-33, 7:1-33. Lidocaine was later incorporated into other DVS-crosslinked HA dermal fillers. For example, in spring 2008, FDA approved Prevelle Silk, a DVS-crosslinked HA dermal filler containing 0.3% lidocaine. EX1002 ¶ 122; EX1020, 8 (periodical announcing FDA approval).

Lidocaine had also been incorporated in a PBCDI-crosslinked HA dermal filler. Anika Therapeutics developed a product called Cosmetic Tissue Augmentation Product (CTA), later renamed Elevess, which contained 28 mg/mL PBCDI-crosslinked HA suspended in a buffer solution with 0.3% lidocaine. EX1050, 1; EX1002 ¶¶ 119-120; *see also* EX1054, 15,886 (publishing approval of CTA). CTA was approved for sale by FDA at the end of 2006, but its composition

was generally disclosed earlier in a 2005 publication. *See* EX1031, 8 (CTA product label identifying the application number of EX1030); EX1002 ¶ 120.

Lidocaine was also included in a DEO-crosslinked HA dermal filler. A 2006 journal article described the clinical trials and characteristics of "Puragen Plus," which included DEO-crosslinked HA and 0.3% lidocaine. EX1012 ("Kinney"), 742; EX1002 ¶¶ 121, 134-135.

In sum, by early 2007—more than a year before the earliest claimed priority date of the Allergan patents—0.3% lidocaine had successfully been incorporated into compositions containing HA crosslinked with three of the four conventional crosslinking agents: DVS, PBCDI, and DEO.[2]



[2] Other parties were developing BDDE-crosslinked HA fillers including lidocaine around the same time as Allergan. EX1002 ¶ 123.

IV. THE CHALLENGED PATENT

Against this backdrop, Allergan began filing applications generally directed towards crosslinked HA (including BDDE-crosslinked) fillers containing lidocaine, including the one leading to the challenged patent. In August and September 2008, Allergan filed a trio of provisional applications to which the challenged patent claims priority. Despite the prior art and commercially available products described above, the patent contends that it had merely "been proposed to incorporate … lidocaine[] into injectable HA-based compositions," EX1001, 2:27-29, without acknowledging this "proposal" had been successfully implemented into several crosslinked HA fillers.

Either disregarding or unaware of the prior art discussed above, the patent alleges "HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time." EX1001, 2:29-34. However, the patent cites no document supporting this assertion.

A. The Challenged Claims

The '202 patent issued with 30 claims; all of which are challenged in this Petition. Each independent claim is a product-by-process claim to a composition comprising BDDE-crosslinked HA, uncrosslinked (or soluble) HA, and lidocaine,

wherein the compositions are made by "providing" the HA components, "adjusting" the pH of the composition, adding the lidocaine, and sterilizing. The independent and dependent claims slightly vary or add known or obvious variations, e.g., the amount lidocaine or uncrosslinked HA.

B. The patent was granted based on proffered "unexpected results"

On February 26, 2009, Allergan filed two similar applications claiming priority to the same three provisional applications. Those application eventually issued as the ancestor '795 and '475 patents. The '202 patent is related to the '475 patent via several continuation applications. Because Allergan's actions during the prosecution of the '795 patents (i.e., the '884 application) led to the granting of the '475 and '202 patents, we summarize that prosecution here.

In the '884 application, the Examiner rejected the claims as obvious over prior art that taught BDDE-crosslinked HA dermal fillers in view of other references disclosing the addition of lidocaine to other dermal fillers. Allergan argued a POSITA would not have expected a lidocaine-containing HA composition could be sterilized by autoclave, EX1023, 25-28, that "it was a surprising and unexpected discovery … that certain [HA] gels … when mixed with lidocaine, could be made to be heat stable and thus useful as dermal fillers." EX1023, 23. At the time of this response, some pending claims were directed to BDDE-crosslinked HA, while others were directed to HA crosslinked with *any* crosslinker. EX1023,

18-20 (claims 51-67). Allergan also argued that a POSITA would have expected that autoclave sterilization would unacceptably reduce the composition's viscosity, thereby making it unsuitable for use as a filler. EX1023, 25. In support of its arguments, Allergan submitted an Inventor's Declaration under 37 C.F.R. § 1.132 stating, among other things, that:

- "It was believed that that adding lidocaine to [HA] gel compositions during manufacturing caused degradation of the [HA] prior to injection;"
- "It was not known whether HA compositions comprising lidocaine were stable or not after high temperature sterilization when placed in storage for any significant length of time;" and
- "It was also believed that the instability of HA described above would have caused a viscosity reduction of the HA that would make it unsuitable for soft-tissue filling applications."

EX1024 ¶¶ 5, 7-8. The inventor did not identify any references or evidence supporting his characterization of what POSITAs supposedly believed "shortly prior to August 4, 2008." EX1024, ¶ 4.

Allergan also submitted a 2012 article (Cui) purportedly teaching that BDDE-crosslinked HA was less heat stable than HA crosslinked with other crosslinkers. EX1025. According to Allergan, Cui further showed that the autoclave stability of the claimed compositions was unexpected. EX1023, 28. But

as explained below (Section VI.D.3, *infra*), none of the crosslinkers described in Cui were actually in use at the time of the patent's filing.

Allergan also cited Example 4 in the specification, arguing that Samples 1, 2, 3, which were described as "non-cohesive HA gels," "showed a substantial reduction in viscosity" after lidocaine was added and the samples were autoclaved. Allergan claimed this viscosity reduction would have been expected by POSITAs. Allergan contrasted those samples with Samples 4, 5, and 6, described as "cohesive gels," alleging they "exhibited a much lower, or even insignificant change in viscosity" after adding lidocaine and autoclaving. EX1023, 26-27.[3]

Relying on Allergan's arguments, the Examiner allowed the'884 application, accepting Allergan's characterization of the state of the art alleged unexpected results:

> Applicant argues that one of ordinary skill in the art would have expected degradation of the [HA] gel with addition of lidocaine during sterilization, *as this was what was known in the prior art*. Applicant unexpectedly found that a [HA] gel cross-linked, but not

[3] This entire Example was present in each provisional application but was deleted from the specification of the '768 application; it is not present in the '202 patent. *Compare* EX1013 (first provisional), 26-27, *with* EX1001, 14:1-36.

> with a non-[HA] biopolymer, mixed with lidocaine and sterilized does not degrade.

EX1023, 9 (emphasis added).

In the ’768 application, claims specifying that the compositions included greater than about 10% uncrosslinked HA were rejected as obvious over U.S. 7,902,171 to Reinmuller, which taught that uncrosslinked HA could suppress injection-related side effects. Allergan argued that the cited references did not disclose the specifically claimed amounts of uncrosslinked HA, and that the skilled person would not have been motivated to use amounts in excess of 10% by volume. EX1033, 59-61. The Examiner issued rejections similar to those made during the prosecution of the ’884 application.

Allergan did not submit the declaration evidence in the ’768 application, but argued in an Examiner interview that it had “unexpectedly found that the addition of lidocaine [to] the filler composition did not cause the composition to become unstable as was expected based on the teachings of the prior art.” EX1033, 12. Even though the declaration and argument were not formally of record in ’768 application, the Examiner’s “Reasons for Allowance” pointed to those unexpected results arguments. EX1033, 8. Even though the declaration and argument were not formally of record in ’768 application, the Examiner plainly relied on the evidence and argument from the’884 application as recounted in the interview.

Allergan filed several continuation applications claiming priority to the '768 application, including what issued as the '202 patent. The Examiner again cited the "unexpected results arguments in copending application" in the Reason's for Allowance. EX1089, 4; *cf.* EX1064, 8 (same in "grandparent" application).

C. Person of Ordinary Skill in the Art

The POSITA at and before the priority date is a scientist involved in the development of dermal fillers, who would have an advanced degree, such as a Ph.D., M.S., or M.D., and several years of experience developing dermal fillers for cosmetic use, including HA-based dermal fillers. The POSITA would be aware of commercially sold dermal fillers, in the United States and abroad, as well as those products for which approvals were being publicly sought. EX1002 ¶ 71-74.

V. CLAIM CONSTRUCTION

Claim terms are construed according to their ordinary and customary meaning as understood by a POSITA and the patent's prosecution history. 37 C.F.R. § 42.100(b). Terms not specifically construed below have their ordinary and customary meaning. Petitioner makes the claim construction order from a civil action involving the grandparent '475 patent of record here. See EX1027. Petitioner also provides a Joint Claim Construction Chart reflecting Petitioner and Allergan's *agreed* constructions in a civil action involving six patents in the same

family. See EX1084, 7-14. Petitioner's proposed constructions are consistent with those adopted by the district court and agreed-upon by Allergan.

A. *sterile*

In both court proceedings, Allergan agreed *sterile* means a composition that is "substantially free of detectable, viable microorganisms." EX1027, 7; EX1084, 6. This is consistent with the specification of the '202 patent. EX1001, 11:33-36.

B. *stable*

The *Medicis* court construed *stable* as "maintains at least one of the following aspects: transparent appearance, pH, extrusion force and/or rheological characteristics, [HA] concentration, sterility, osmolarity, and lidocaine concentration." EX1027, 11. Allergan *agreed* to the same construction in the litigation against Petitioner Prollenium. EX1084, 5. The '202 patent defines the terms *autoclave stable* and *stable to autoclaving* in the same way. EX1001, 4:51-58. The Board should adopt the parties' agreed construction. Petitioner also contends trial should be instituted under the Board's "more detailed definition" adopted in prior institution decisions. *See*, *e.g.*, IPR2019-01508, Paper 19, 13 (citing IPR2017-01906, Paper 15, 9-10 (Mar. 9, 2018)). Allergan's assent to this proposed construction here was not part of the record in any prior proceeding.

C. *uncrosslinked HA* or *soluble form HA*

The *Medicis* court construed *uncrosslinked HA* to mean "water soluble HA (i.e., uncrosslinked HA and/or lightly crosslinked HA)," in accordance with the specification's definition of the term *free HA*. EX1027, 21; EX1001, 5:15-23. The parties here agreed to the same construction for all the soluble HA terms in the underlying litigation. EX1084, 4; see also EX1001 5:19-20 ("Free HA generally remains water soluble."). This construction should be used here as well.

D. *made by a process comprising*

Every claim is in the form of a product-by-process claim, i.e., a product prepared by a certain process. When considering patentability of a product-by-process claim, the focus is on the product—not the process of making it. *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). A process limitation only imparts patentable weight to the claim if the resulting (i.e. claimed) product has "structural and functional differences" that distinguish the claimed product from the prior art. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

All the claims cover processes in which pH of the BDDE-crosslinked filler is adjusted above about 7.5, and in the sole example describing the addition of lidocaine to an HA composition (Example 2), the pH is adjusted to between about 7.5 to about 8. EX1001, 13:21-22. The addition of 0.3% lidocaine HCl then lowers the pH of the gel[4] to "about 7." EX1001, 13:22-26. The pH 7 mixture is loaded into a syringe and sterilized using an autoclave, resulting in a stable product having acceptable "viscosity, cohesivity, and extrusion force." EX1001, 13:36-45. Although the '202 patent does not disclose any alternative processes for combining lidocaine and a BDDE-crosslinked filler, there is no data or statement supporting a proposition that the claimed sequence of pH adjustment and lidocaine addition imparts any meaningful structural or functional characteristics to the resulting fillers. EX1002 ¶ 149.

[4] Example 2 in the patent indicates that "free HA gel may be added to the HA/lidocaine gel mixture"—i.e., after adding lidocaine. EX1001, 13:30-31. There is no description of adding free HA in the *before* pH adjustment or lidocaine addition. On the other hand, every claim requires "adjusting the pH" of an HA component or mixture comprising crosslinked *and* uncrosslinked/"soluble form" HA. It appears the specification does not exemplify the claimed process.

Allergan has conceded through its arguments and disclosures that the pH-adjustment step is not necessary to obtain sterile, stable fillers. For example, during prosecution of the '884 application, Allergan argued that one sample was "stable and had similar viscous and elastic properties … when prepared with lidocaine, both with *and without* pH control"—i.e., without adjusting the pH. EX1023, 27 (emphasis added).[5] In the same response, Allergan amended the specification of the application to state that a different sample's "viscous and elastic properties … changed an *insubstantial amount*" when prepared with "no pH adjustment." EX1023, 12 (emphasis added). Thus, according to Allergan, fillers with "similar viscous and elastic properties" can be obtained regardless of whether the pH is adjusted. Thus, the differences between products prepared according to the claimed process (with pH adjustment) and products prepared according to other, non-claimed processes (without pH adjustment) are *insubstantial*.[6] As such,

[5] The provisional application contains similar disclosure. See EX1013, 26-27 ("Sample 6 is … stable to autoclaving" when prepared with and without pH adjustment).

[6] The Office's "Reasons for Allowance" only referenced the composition and proffered "unexpected results," with no mention of the recited process steps. EX1089, 4.

Allergan cannot now argue that the claimed process steps produce unique fillers having meaningful structural or functional difference compared to obvious fillers made by other processes.

E. *adjusting the pH of the HA component to an adjusted pH above about 7.2*

The plain meaning of "adjusting" is to "modify" or "alter." There is no "starting" pH required by any claim, so there is no limitation in which *direction* the pH is adjusted (up or down). The patent includes an Example where the pH of the HA component is *increased* from a "substantially neutral pH" (about 7.2) to between about 7.5 and about 8. EX1001, 13:14-22. But a preference in an example is not a clear and unmistakable disclaimer of processes in which the pH is *decreased*. *Cont'l Circuits LLC v. Intel Corp.*, 915 F.3d 788, 797-799 (Fed. Cir. 2019). So, according to the plain meaning of *adjusting*, the claims embrace processes where the HA component has a starting pH above 7.2 and the pH is adjusted *downwards* to some value (still) above about 7.2 (claim 1) or 7.5 (claim 5). *See also* EX1002 ¶¶ 137-138, 140.

VI. CLAIMS 1-30 ARE UNPATENTABLE

The '202 patent claims sterile, stable dermal fillers containing BDDE-crosslinked HA, uncrosslinked (or soluble form) HA, and lidocaine. Before the relevant filing date, POSITAs had already combined lidocaine with each of the other clinically used crosslinked HA fillers (i.e., DVS, DEO, and PBCDI-

crosslinked HA compositions). Adding lidocaine to a BDDE-crosslinked HA filler represented the most natural and obvious next step. Moreover, while the claimed pH adjustment steps are not relevant to the patentability, those steps, as well as the other process limitations in the '202 patent, are obvious over the prior art as well.

The only other feature present in the claims—the particular amount of uncrosslinked HA—was a well-known design choice. POSITAs often varied the amount of uncrosslinked HA in a filler to achieve desired flow properties. The specific amounts of uncrosslinked HA recited in the challenged claims reflect conventional amounts already used in known fillers. However, to further demonstrate the claims' unpatentability, ancillary references Clark and Smith are included in the Grounds to underscore that the *specifically claimed* amounts of free HA were known and clinically used before the priority date.

A. References Relied Upon

1. Lebreton

Lebreton shares the same inventor as the challenged patent and discloses BDDE-crosslinked HA dermal filler compositions. The challenged patent cites Lebreton when explaining how selection of various HA components in dermal fillers was known to affect characteristics such as extrusion force, elastic modulus, and viscous modulus, among others. EX1001, 8:54-64.

Lebreton discloses dermal fillers obtained by crosslinking a mixture of low and high molecular weight HA starting materials, and claims they have improved properties relative to fillers using a single type of HA. EX1029 ¶¶ [0021-0024]. Lebreton teaches that the fillers can be formulated at pH preferably between 7 and 7.4 (more preferably between 7.1 and 7.3), and that the pH can be controlled using the appropriate buffer solution. EX1029 ¶ [0049].

Lebreton discloses two examples in which a mixture of high molecular weight and low molecular weight HA is crosslinked with BDDE in the presence of 0.25 N sodium hydroxide, i.e., at a pH greater than about 10.[7] The resulting mixture is neutralized to pH 7.2 using a phosphate buffer and dialyzed. The product is mechanically homogenized, loaded into a syringe, and sterilized in an autoclave. EX1029 ¶¶ [0080-0092].

2. Sadozai

Sadozai discloses PBCDI-crosslinked HA dermal fillers that include lidocaine. EX1030 ¶¶ [0007, 0084-0085]; EX1002 ¶ 132. Sadozai teaches that the dermal fillers may include an anesthetic that can increase the stability of the dermal filler relative to an equivalent filler *without* the anesthetic:

[7] The pH of 0.25 N NaOH is approximately 13.4 [14 – log(0.25)]. Adding sodium hyaluronate would not decrease the pH by over 3 pH units. EX1002 ¶ 170.

> [T]he storage modulus G' is increased, e.g., the composition is stabilized, by the inclusion of a local anesthetic, e.g., lidocaine, compared to a non-stabilized composition, e.g., an identical composition except that the local anesthetic is not included.

EX1030 ¶ [0068].

Sadozai discloses several examples in which one of the PBCDI-crosslinked HA samples (Example 5) is reconstituted in a phosphate buffer containing 0.3% lidocaine hydrochloride (Example 12, 17, and 18 employ Buffer 4). EX1030 ¶¶ [0084, 0090, 0099-104]. Each of the resulting gels are loaded into a syringe and autoclaved. Sadozai teaches that the storage modulus (which relates to viscosity) of the lidocaine-containing crosslinked HA after autoclaving was higher than the same crosslinked HA without lidocaine. EX1030 ¶¶ [0090, 0107]; *see* EX1002 ¶ 133 (relating storage modulus to viscosity).

3. Kinney

Kinney describes a clinical study comparing two dermal fillers: Restylane, which had been on the market for several years, and Puragen Plus, which was undergoing FDA clinical trials. EX1012, 741-742. Kinney teaches Restylane is an injectable dermal filler containing 20 mg/mL of BDDE-crosslinked HA particles with a high concentration of "minimally modified HA molecules." EX1012, 741-742. Kinney notes that a "major disadvantage" of existing HA based fillers was the pain that accompanied injection. EX1012, 741.

Kinney also teaches Puragen Plus, a dermal filler containing 20 mg/mL of DEO-double crosslinked HA particles, lidocaine hydrochloride (0.3%), and what a POSITA would recognize as a pH buffer component, which was undergoing clinical trials. EX1012, 742; EX1002 ¶ 135. Kinney teaches that injection with Puragen Plus caused minimal or no pain for patients. EX1012, 747.

4. Zhao

Zhao describes double-crosslinked HA dermal fillers with improved biostability relative to single-crosslinked HA. *See* EX1058 ¶¶ [0014], [0058]. Zhao describes an example in which double-crosslinked HA was prepared by first crosslinking HA with DEO under alkaline conditions, followed by crosslinking the resultant product with DEO under acidic conditions. EX1058 ¶ [0032]. Zhao teaches that a number of crosslinking agents—including both BDDE and DEO—can be used to prepare double-crosslinked HA using the described methods. EX1058 ¶ [0019-0021].

5. Narins

Narins is a 2005 journal article describing characteristics of several FDA-approved dermal fillers. EX1007, 151, 153. Narins includes a description of the same Restylane product disclosed by Kinney and teaches that Restylane is heat sterilized in its final container and has a shelf life of 1.5 years from date of manufacture. EX1007, 156.

6. Smith

Smith is a 2007 journal article describing the products Juvéderm Ultra and Juvéderm Ultra Plus. Smith teaches Juvéderm has been clinically used in Europe since at least 2003 and was introduced in the U.S. in 2007. EX1009, 67S. Smith teaches Juvéderm is crosslinked with BDDE and is formulated with "about 10% of non-crosslinked [HA] … to optimize the flow properties of the material" and that other available dermal fillers had "a considerably larger amount of free [HA]" than Juvéderm, "typically around 20 percent." EX1009, 72S.

7. Clark

Clark is a 2007 journal article comparing several physical characteristics of HA dermal fillers that "can be used to make clinical decisions with regard to product choice." EX1008, 28S. Clark teaches the dermal filler market requires a variety of products with varying characteristics because "no single filler product is suitable for all patients and all anatomic applications." EX1008, 31S. Regarding soluble (or "free") HA, Clark discloses that crosslinked HA fillers Hylaform and Restylane included about 4% and 25% soluble HA, respectively. EX1008, 29S.

B. Grounds 1–2: Claims 1-30 are obvious over the combination of Lebreton and Sadozai in view of Clark or Smith

Lebreton describes a BDDE-crosslinked HA filler. By August 2008, lidocaine (at 0.3 wt.%) had been incorporated in a range of dermal fillers to mitigate injection pain. EX1002 ¶¶ 119-122, 128-135. Uncrosslinked (or soluble

form) HA, including amounts of 10%, and 25%, had been included in HA fillers to optimize injection characteristics. EX1002 ¶¶ 93-96; EX1008, 29S; EX1009, 67S. Merely adding lidocaine and free HA in conventional amounts to a prior art filler—which the provisional applications demonstrate is all that Allergan did—is not inventive. *Cf.* EX1013, 26-27 (describing mixing Juvéderm Ultra Plus with lidocaine, adjusting pH to 7.2, and observing the mixture can be autoclave sterilized).

In Grounds 1-2, the combination of Lebreton and Sadozai produces a soft tissue filler meeting all the limitations of the challenged claims except for the specifically claimed amounts of uncrosslinked (or soluble form) HA. As explained above, Clark and Smith disclose clinically approved fillers containing specific amounts of uncrosslinked HA falling within the challenged claims.[8] The POSITA would have been aware of these other fillers, and would have reasonably expected that similar amounts of uncrosslinked HA could be used in the modified filler described below.

[8] Allergan has argued that Clark and Smith were merely cumulative of references considered by the Examiner. EX1088, 20. They are not. While Allergan argued that the then-cited art did not teach at least 10% uncrosslinked HA, Clark and Smith both explicitly disclose these amounts. EX1033, 59-61.

1. Motivation to Combine

Lebreton discloses BDDE-crosslinked dermal fillers said to have improved properties over earlier BDDE-crosslinked fillers. The POSITA would have been aware that injection pain was a drawback for these products (EX1002 ¶ 117) and would have been motivated to apply the same solution that had been successfully employed with other injectable fillers—the incorporation of lidocaine. Sadozai exemplifies such a solution.

As shown in Section III.C above, lidocaine had been successfully incorporated into compositions containing HA crosslinked with the three other conventional crosslinking agents: DVS, PBCDI, and DEO. Two products had already received FDA approval by the challenged patent's earliest filing date. EX1020, 8 and EX1052 (Prevelle Silk); EX1019, 4 (Anika's Elevess, an implementation of Sadozai; EX1002 ¶ 120). A third (Puragen Plus) was approved in Europe and undergoing clinical trials in the U.S. *See* EX1012, 742; EX1002 ¶¶ 121, 134-135. A composition containing BDDE-crosslinked HA and lidocaine was a derivative and predictable next step in view of the success of the other three clinically used crosslinkers. At minimum, adding lidocaine to Lebreton would have been obvious to try.

Moreover, the prior art suggests a reasonable expectation of success that adding lidocaine to Lebreton would produce a lidocaine-containing dermal filler.

The repeated successful use of lidocaine across the remaining spectrum of crosslinked HA dermal fillers would have prompted a POSITA to—at minimum—attempt the combination. DVS, PBCDI, and DEO crosslinked HA gels share many more similarities with BDDE-crosslinked gel than differences. EX1002 ¶ 209. Once crosslinked, all four crosslinkers are devoid of reactive or unstable functional groups which a POSITA might suspect would unfavorably react in the presence of lidocaine. EX1002 ¶ 209.

Further, lidocaine had been successfully incorporated into dermal fillers containing more significant chemical differences than the crosslinked-HA fillers discussed above. In the cosmetic field alone, lidocaine had been successfully incorporated into fillers based on synthetic polymers, bovine collagen, and human collagen. EX1002 ¶ 117. There is no credible reason why the POSITA would have not expected success in incorporating lidocaine into BDDE-crosslinked HA as well. Even if there had been some uncertainty whether lidocaine could be added to BDDE-crosslinked HA (and there was not), absolute certainty is not necessary for a proposed modification to be obvious. EX1002 ¶¶ 208-214. *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1075 (Fed. Cir. 2019) (affirming PTAB's finding of reasonable expectation of success even though the "effect in combination may have been uncertain at the time"); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be

reasonable, not absolute"). Nothing in the prior art suggested any difficulty combining lidocaine with a BDDE-crosslinked HA, such as taught by Lebreton.[9]

The POSITA also would have been well-aware that uncrosslinked HA had been included in crosslinked HA fillers to optimize the injectability of a gel, among other reasons. EX1002 ¶¶ 93-96; EX1022, 79; EX1008, 29S; EX1009, 67S. The POSITA would have understood that increasing concentrations of uncrosslinked HA decreased the required extrusion force (EX1002 ¶¶ 93-94). Accordingly, the uncrosslinked HA concentration is a result-effective variable. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012) ("A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective."). It is routine, and obvious, to optimize a result-effective variable. *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable … is ordinarily within the skill of the art."). Clark and Smith discuss available products that teach such known, useful concentrations of uncrosslinked HA and provide further direction for the POSITA designing a dermal filler. EX1002 ¶ 143.

[9] As noted in Section VI.D.1, below, Allergan's declaration in the prosecution of a related application proffering "unexpected results" cited no prior art to substantiate the claim.

The POSITA could have easily adapted the procedure disclosed in Lebreton to incorporate lidocaine into the BDDE-crosslinked gels. In particular, Lebreton teaches that after the crosslinking reaction, the resulting gel is dialyzed with a pH 7.2 phosphate buffer. EX1029 ¶ [0070]. The POSITA could have easily incorporated lidocaine into the buffer solution at a concentration of 0.3% (such as taught by Sadozai), thereby obtaining a pH 7.2 BDDE-crosslinked gel containing lidocaine. EX1002 ¶¶ 147-148.

The POSITA would have then mechanically homogenized the gel into particles (EX1002 ¶ 150), and, to the extent the desired amount of free HA was not already present in the composition, added free HA. The POSITA would have loaded the composition into a syringe, and sterilized it using an autoclave to obtain at the claimed composition. *See* EX1029 ¶ [0070]; EX1002 ¶¶ 150, 174, 191, 199.

2. Detailed claim analysis

Independent claim 1 includes most of the common features of the other independent claims, and dependent claims 2-8 include features that are included in other challenged claims. Prollenium presents these claims first to illustrate how the prior art teaches those limitations. Other claims are shown obvious by reference to the corresponding limitations in claims 1-8 and are obvious for the same reasons.

a. Claims 1 and 5

(i) [1.pre] *A stable, sterile soft tissue filler comprising:*

Lebreton and Sadozai both teach dermal fillers. EX1029 ¶ [0005]; EX1030 ¶¶ [0007, 0012] (HA "effective for tissue augmentation"). "Stable" compositions include those that maintain sterility over a length of time (*See* V.B). Lebreton teaches the BDDE-crosslinked gel is sterilized in its final container (EX1007, 156); the POSITA would understand that the product would remain sterile indefinitely so long as the final container was not opened. EX1002 ¶¶ 150, 172-174.

(ii) [1.1.1] *a hyaluronic acid (HA) component comprising HA crosslinked with [BDDE]*

Lebreton discloses BDDE-crosslinked HA. EX1029 ¶¶ [0068-0076].

(iii) [1.1.2] *and uncrosslinked HA, wherein the HA component comprises greater than about 10% uncrosslinked HA by volume*

Crosslinked-HA fillers were known to incorporate uncrosslinked or "free" HA in varying amounts. **Smith** (Ground 1) discloses that existing, known crosslinked-HA fillers (including Allergan's non-lidocaine Juvéderm product) incorporated free HA in varying amounts. EX1009, 67S, 72S. For example, Allergan's non-lidocaine Juvéderm contained about 10% uncrosslinked HA, while other products had around 20% uncrosslinked HA. EX1009, 67S, 72S. **Clark** (Ground 2) discloses BDDE-crosslinked Restylane included 25% uncrosslinked HA. EX1008, 29S (Table 1).

The POSITA knew that the amount of uncrosslinked HA could be varied to "optimize the flow properties" of a crosslinked gel. EX1009, 67S; *see also* EX1022, 78 (teaching free HA is a "lubricant for flow characteristics"). The POSITA would have been motivated to include uncrosslinked HA and could have easily optimized the amount to obtain a desired extrusion force, including amounts greater than about 10% by volume. EX1002 ¶¶ 143-145.

(iv) [1.2] lidocaine at a concentration of about 0.3% by weight of the soft tissue filler combined with the HA component;

Sadozai teaches crosslinked HA fillers with a buffer solution including 0.3% lidocaine. EX1030 ¶ [0084, 0090, 0107]; *see also* EX1002 ¶ 142 (explaining this was a common concentration and effective to mitigate pain). The POSITA could have added this solution to the BDDE-crosslinked fillers taught by Lebreton. EX1002 ¶ 147.

(v) [1.3] Process steps of claim 1

As discussed in Section V.D, the claimed process steps are not entitled to patentable weight. Nevertheless, the combination of Lebreton and Sadozai expressly disclose most of the recited process steps, as generally shown immediately above:

Process Steps of claim 1	
[1.3.1] providing the HA component;	See [1.1.1][10]
[1.3.2] adjusting the pH …	See discussion below.
[1.3.3] adding a solution containing lidocaine to the HA component having the adjusted pH to obtain a soft tissue filler; and	See [1.2]
[1.3.4] heat sterilizing the soft tissue filler to obtain a stable, sterile soft tissue filler.	See [1.pre]

The only recited step not expressly disclosed is that of "adjusting the pH" before adding the lidocaine-solution. The process steps are not entitled to patentable weight because they do not add any meaningful structural or functional difference over the proposed combination as described above, but even if they did the recited steps are nevertheless obvious.

(a) The adjusting step is not entitled to patentable weight

Process limitations are generally not given any patentable weight in an obviousness analysis. *See* Section V.D. While an exception is applied when the claimed process steps imparts meaningful structural and functional differences in the product, such is not the case here. In particular, there are no meaningful

[10] Each bracketed limitation or claim reference (such as in this table) is a clickable-hyperlink to the cited discussion in the PDF version of this paper.

differences between fillers produced by the claimed process and fillers produced according to the combination of Lebreton and Sadozai.

In each of Lebreton's examples, after neutralization and purification at pH 7.2, the BDDE-crosslinked fillers are packed in syringes and autoclave sterilized. *E.g.*, EX1029 ¶¶ [0070], [0076]. The POSITA would have been motivated to use the same pH for the modified filler, and as explained above would have added lidocaine in a pH 7.2 buffered solution, as taught by Sadozai. EX1002 ¶ 147 (citing EX1030 ¶¶ [0084]). In other words, the POSITA would have prepared the pre-sterilization, lidocaine-containing fillers at the same pH taught by Lebreton, 7.2. The POSITA would have then packed the composition in a syringe and autoclaved it as in Lebreton. EX1002 ¶ 150. In this hypothetical composition/process, the pH of the filler remains substantially the same before and after the addition of the lidocaine. EX1002 ¶ 151.

In the claimed process on the other hand, the pH is adjusted (for instance above about 7.5) and then lidocaine is added, lowering the pH to (for instance) about 7.2. EX1001, 13:18-26. While HA can be degraded at high or low pH, or at elevated temperature, HA is stable at room temperature or less in solutions at pH between 5 and 9, and certainly between 6.5 and 8. EX1086, Abstract; EX1087, 67; EX1002 ¶ 159. So there would not be any meaningful degree of crosslinked-HA degradation during the claimed pH adjustment. EX1002 ¶¶ 159-160. In other

words, the physical structure of the HA would not be meaningfully changed in the claimed process compared to a process where lidocaine was added in a buffered solution (and the pH does not change at all). EX1002 ¶ 160.

Because the HA would not meaningfully change during lidocaine addition, either by the claimed process or by the process suggested by Lebreton and Sadozai, the pre-sterilization compositions produced by either method would not be meaningfully different. EX1002 ¶ 161. Consequently, the post-sterilization products would also not have any meaningful differences. EX1002 ¶ 162. There would not be any structural or functional features differentiating the claimed fillers from those produced according to the compositions taught by Lebreton and Sadozai.

(b) Allergan has admitted different processes do not produce meaningfully different fillers

Additionally, as explained in Section V.D above, Allergan's arguments and disclosures (in related patents) concede that multiple supposedly inventive embodiments of the invention either do not require or are only "insubstantial[ly]" affected by the recited pH adjustment step. There are no limitations in any of the claims of the patent excluding these embodiments from the scope of the claims or otherwise distinguishing the claimed fillers from fillers claimed in related patents. Since it is clear from Allergan's own statements that the pH adjustment step is not

necessary to obtain sterile, stable fillers, the claims should be evaluated without regard to the claimed pH adjustment step.

(c) Even if entitled to any weight, the pH adjustment is obvious

Leaving aside that the claimed steps do not impart unique features onto the product, the claimed pH adjustment step (including in the upwards direction exemplified in the specification) is still obvious. The POSITA would have been motivated to prepare a composition having the same pre-sterilization pH as the compositions described by Lebreton, e.g., 7.2. *E.g.*, EX1029 ¶¶ [0048, 0070, 0076]; EX1002 ¶ 146. When incorporating lidocaine, the POSITA would have used a solution containing lidocaine HCl,[11] as the hydrochloride salt was commonly used when preparing lidocaine-containing dermal fillers. EX1002 ¶ 147; EX1030 ¶ [0084]; *see also, e.g.*, EX1012, 742; EX1059 7:5-10. The POSITA would have known that lidocaine HCl was weakly acidic and that adding it directly to Lebreton's gel would lower the pH below the desired 7.2. EX1002 ¶¶ 151, 163.

With a target pH of 7.2 in mind, the POSITA would have known to account for the reduction in pH caused by introducing acidic lidocaine HCl in the composition. EX1002 ¶ 163. A POSITA would have known that a limited number

[11] A "solution containing lidocaine" includes solutions containing lidocaine HCl. EX1001, 6:40-41.

of simple strategies could be used to account for the effect of lidocaine HCl on the pH of the composition so as to arrive at a composition having a target pH of 7.2:

(a) adding lidocaine HCl (thereby lowering the pH below the target pH of 7.2) then adding a base to increase the pH back to the target pH of 7.2;

(b) raising the pH above the target pH of 7.2 and then adding lidocaine HCl to lower the pH to the target pH of 7.2; or

(c) buffering the lidocaine HCl at the target pH of 7.2 and then adding the buffered lidocaine composition to the crosslinked HA composition (such that the pH remains at the target pH of 7.2 throughout the course of the lidocaine addition).

Sadozai expressly teaches the third option (EX1030 ¶ [0090]), and POSITAs could have easily explored the other two. EX1002 ¶ 164. As there are only a finite number of possibilities for combining lidocaine HCl with the BDDE-crosslinked composition taught by Lebreton, the POSITA would have been motivated to explore them all.[12] EX1002 ¶ 165.

[12] While there are numerous specific processes that could be used, the claims are extremely broad, only requiring a pH adjustment.

(vi) [claim 5]

Claim 5's additional (purported) limitation that the pH is adjusted "above about 7.5" is likewise obvious. The difference in pH between above about 7.2 (in claim 1) and above about 7.5 in claim 5 is minor—as explained above there is no meaningful chemical difference between HA at a pH above about 7.2 and HA above about 7.5, it is simply a difference in degree that does not impart any patentable distinction. EX1002 ¶ 166. The '202 patent indicates that adding lidocaine HCl to a BDDE composition at pH 7.5 to 8 results in a final pH of about 7. Allergan has also produced a document (in an opposition proceeding for a related EPO patent) indicating that the pH of a filler formulated at pH = 7.2 is reduced to 6.8 when combined with 0.3% lidocaine hydrochloride. EX1085, 3. If the POSITA was targeting a final pH of about 7.2, routine optimization would necessarily lead to a pH adjustment to above about 7.5. EX1002 ¶ 167.

Having obtained the lidocaine-containing filler at physiological pH, the skilled person would have then sterilized the product in a sealed syringe. EX1002 ¶ 150. The filler would remain sterile (i.e., stable) so long as the packaging was not opened. EX1002 ¶ 150.

b. Independent claims 9, 17, and 25

Independent claims 9, 17, and 25 are generally similar in scope to claim 1, with minor variations in recited features. Every element of these claims is

presented in the table below, combined in rows to show identical (or nearly so) limitations across these claims, with reference to the corresponding limitation and prior art disclosure in claim 1.

Claims 9, 17, 25	
[9.pre] A stable, sterile soft tissue filler comprising: [17.pre] and [25.pre] *(identical)* A sterile, stable injectable soft tissue filler composition comprising:	See [1.pre] To the extent "injectable" in claims 17 and 25 is a limitation, Lebreton and Sadozai's gels are injectable. EX1029 ¶ [0007]; EX1030 ¶ [0012].
[9.1.1] a hyaluronic acid (HA) component comprising HA crosslinked with [BDDE] [17.1.2] *and* [25.1.2] *(identical)* [a mixture of] crosslinked HA … being crosslinked with [BDDE]	See [1.1.1]
[9.1.2] and uncrosslinked HA; and [17.1.1] *and* [25.1.1] *(identical)* a mixture of soluble form hyaluronic acid (HA),	See [1.1.2] and Section V.C (arguing same meaning for "uncrosslinked" and "soluble form" HA)
[9.2] lidocaine at a concentration of about 0.3% by weight of the soft tissue filler combined with the crosslinked HA component; [17.1.3] *and* [25.1.3] *(identical)* lidocaine in an amount effective to mitigate pain upon injection of the composition … [25.2] the lidocaine of the mixture being present in a concentration of about 0.3% by weight of the composition;	See [1.2]

Claims 9, 17, 25	
[9.3] wherein the soft tissue filler is stable after heat sterilization at between about 120° C. and about 130° C.;	Discussed below
[9.4] wherein the soft tissue filler has a pH of about 7; and	Lebreton teaches its gel is "buffered to a pH compatible with the human," which it teaches is "between 6.5 and 7.5, advantageously between 7 and 7.4 and very advantageously between 7.1 and 7.3." EX1029 ¶ [0048]. The POSITA could have selected any pH within this range, including pH 7, instead of the exemplified pH 7.2. EX1002 ¶ 171-173. Allergan has not alleged or demonstrated any criticality or unexpected results associated with the claimed pH over any other physiologically appropriate pH.
[17.2] the composition having a HA concentration of between about 20 mg/ml and about 30 mg/ml;	Lebreton discloses a mixture of HA "at a concentration … advantageously between 20 and 30 mg/g," which is the same concentration claimed. EX1029 ¶ [0049]; EX1002 ¶ 176-78.
[9.5] wherein the stable, sterile soft tissue filler is made by a process comprising: [17.3] *and* [25.3] *(identical)* wherein the sterile, stable injectable soft tissue filler composition is made by a process comprising:	See [1.3]
[9.5.1] providing the HA component crosslinked with BDDE [17.3.1] *and* [25.3.1] *(identical)* providing the soluble form HA and crosslinked HA;	See [1.3.1]

Claims 9, 17, 25	
[17.3.2] adjusting the pH of the soluble form HA and crosslinked HA; [25.3.2] adjusting the pH of the soluble form HA and crosslinked HA to an adjusted pH above about 7.2;	See [1.3.2][13]
[9.5.2] adding a solution containing lidocaine to the HA component crosslinked with BDDE to obtain a soft tissue filler; and [17.3.3] *and* [25.3.3] *(identical)* adding a solution containing lidocaine to the soluble form HA and crosslinked HA having the adjusted pH to obtain a HA-based injectable soft tissue filler composition; and	See [1.3.3]
[9.5.3] heat sterilizing the soft tissue filler to obtain a stable, sterile soft tissue filler. [17.3.4] *and* [25.3.4] *(identical)* heat sterilizing the HA-based injectable soft tissue filler composition to obtain the sterile, stable injectable soft tissue filler composition.	See [1.3.4]

(i) element [9.3] (sterilization)

Lebreton's gel is "packed into syringes and sterilized in an autoclave by means of moist heat." EX1029 ¶ [0070]; *see also* EX1030 ¶ [0054]. The POSITA would have been motivated to heat-sterilize the lidocaine-containing gel under

[13] The "adjusting" pH step is not included in independent claim 9.

conventional sterilization conditions. *See* EX1002 ¶¶ 173-174; EX1038 ¶¶ [0070], [0085], [0088] (disclosing sterilization of DVS-crosslinked HA by autoclaving at 121°, 126°, or 131° C); EX1041, 111 (disclosing sterilization of HA gel by autoclaving at 121° C); EX1042 ¶ [0091]; EX1030 ¶ [0054] (disclosing sterilization of PBCDI-crosslinked HA by autoclaving at 120-140° C). Merely reciting a range of conditions known to be effective to sterilize an otherwise obvious composition, and observing the inherent effect of such sterilization, cannot confer patentability. *In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (holding the discovery of an inherent feature will not confer patentability on an otherwise obvious composition).

c. Dependent claims 13, 21 and 27

Claims 13, 21 and 27 depend from independent claims 9, 17 and 25, respectively. Each of claims 21 and 27 further recite that the "adjusting the pH" process step adjusts the pH to "above about 7.5."[14] This purported limitation is not patentable for the same reason as discussed above for claim 5 (and element [1.3.2]).

[14] Independent claim 9 lacks the "adjusting the pH" step; claim 13 adds the "adjusting" step itself.

d. Dependent claims 2-4, 10-12, 18-20, 26

Dependent claims 2-4, 10-12, 18-20 are identical, apart from the specific claim from which each depends and which of the equivalent terms for uncrosslinked HA is used (i.e., uncrosslinked HA or soluble form HA).

(i) amount of uncrosslinked HA claims

Claims 2, 10, and 18 recite that the composition comprises "at least about 15% [uncrosslinked/soluble form] HA by volume," and **claims 3, 11, and 19** increase the amount to "at least 20%" uncrosslinked HA by volume. Clark teaches Restylane has 25% uncrosslinked HA, within the range of each of those claims. EX1008, 29S (Table 1).

Claim 26 recites that soluble form HA is "about 10% to about 20% by volume." Ground 2 renders claim 26 unpatentable over Smith because the a POSITA could have selected (at least) any amount between 10-20% while optimizing the flow characteristics of the filler. EX1009, 67S, 72S; *see also* EX1002 ¶ 180.

(ii) "particles … in a relatively fluidic medium" claims

Claims 4, 12, and 20 each recite that the mixture of crosslinked and uncrosslinked HA comprises "particles of crosslinked HA in a relatively fluidic medium of [uncrosslinked/soluble form] HA." Allergan's provisional application admits that the prior art Restylane composition "compris[es] particles of crosslinked HA material dispersed in a carrier of uncrosslinked HA material."

EX1013, 19. Allergan's description of Restylane is consistent with Dr. DeVore's experience and his opinion of the literature. EX1002 ¶¶ 106, 169.[15] Thus, Allergan *admits* that the limitation of claim 9 exists in the prior art Restylane product. As explained by Dr. DeVore, a product otherwise like Restylane (BDDE-crosslinked HA and ~25% uncrosslinked HA) but including 0.3% lidocaine would be expected to have the same gross structural features—particles of crosslinked HA in a fluidic medium of uncrosslinked HA. EX1002 ¶ 169.

e. Dependent claims 6-8, 14-16, 22-24, 28-30

Dependent claims 6-8, 14-16, 22-24, 28-30 are identical, apart from the specific claim from which each depends. Each of them recites a step of "providing dry uncrosslinked NaHA material and hydrating the dry uncrosslinked NaHA material in an alkaline solution to obtain an alkaline [uncrosslinked] NaHA gel." Although the process steps should not be taken into account in an obviousness analysis (*see* Section V.D above), the claimed process steps are nonetheless obvious.

[15] *See also* EX1012, 741-742 (describing Restylane as containing BDDE-crosslinked "HA particles with a high concentration of minimally modified HA molecules").

Lebreton teaches the same process of hydrating dry NaHA fibers in an alkaline (0.25 N NaOH) solution to obtain an NaHA gel, prior to adding BDDE and crosslinking. EX1029 ¶¶ [0068, 0074]. Dr. DeVore calculated the pH of the NaOH solution to be greater than about 10. EX1002 ¶ 170. The POSITA would have been motivated to use this same process. EX1002 ¶ 170. Thus, each of the above claims are obvious.

C. Grounds 3-4: Claims 1-30 are obvious over the combination of Kinney, Narins, and Zhao in view of Clark or Smith

Kinney teaches a double-DEO crosslinked HA filler that includes 0.3 wt.% lidocaine to afford "relatively pain-free injection." EX1012, 742. Kinney states that the double-crosslinking provides advantages including improved stability during sterilization and enhanced stability and slower degradation in vivo. EX1012, 742. Zhao teaches double-DEO crosslinked HA, and that BDDE crosslinks are interchangeable with DEO. EX1058 ¶ [0019]. Given the market preference for BDDE-crosslinked HA fillers, it would have been obvious to simply substitute the DEO crosslinker in Kinney with BDDE (as taught by Zhao) and sterilize the resulting composition using the conventional conditions taught by Narins.

1. Motivation to Combine

Kinney and Narins teach that Restylane, which contained both particles of single-BDDE-crosslinked HA and free HA, was an established dermal filler, but its injections were painful due to lack of lidocaine. EX1012, 741; EX1007, 156.

Kinney also discloses Puragen Plus, which included particles of double-DEO crosslinked HA filler, and that patients preferred it over Restylane because it contained lidocaine. EX1012, 746. The POSITA would have been motivated to exchange the DEO crosslinker in Puragen Plus with a BDDE-crosslinker, as BDDE-crosslinked fillers were already established in the marketplace and approved by FDA. EX1002 ¶ 183.

As explained in Section VI.B.1, the POSITA would also have been aware that free HA had been included in crosslinked HA fillers to optimize the injectability of a gel, and that the concentration of free HA is a result-effective variable that was routinely optimized based on known, useful concentrations such as taught in Smith and Clark.

A POSITA could have easily made particles of double BDDE-crosslinked HA based on the teachings of Zhao. Zhao discloses processes to prepare double crosslinked HA (EX1058 ¶¶ [0083-0093]), including double BDDE-crosslinked HA. EX1058 ¶ [0019]. Because BDDE and DEO are each bis-epoxide crosslinkers, the POSITA would have reasonably expected that Zhao's process could be adapted to use BDDE instead of DEO. EX1002 ¶ 183-184. Moreover, given that BDDE and DEO are chemically similar, a POSITA would reasonably expect that lidocaine would function analogously in both of the crosslinked gels. EX1002 ¶ 185; *Hoffmann La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed.

Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.").

2. Detailed claim analysis

a. Claims 1 and 5

(i) [1.pre] *A stable, sterile soft tissue filler comprising:*

Kinney teaches sterile, soft tissue fillers. EX 1012, 741-742 ("The ester bonds confer increased stability…during sterilization"). Narins teaches that Restylane is heat-sterilized in its final container (EX1007, 156) and the POSITA would have used the same technique for the sterilization of the as-modified composition. EX1002 ¶ 191. As explained in Section VI.B.2.a(i), the POSITA would have necessarily obtained a stable filler in so sterilizing.

(ii) [1.1.1] *a hyaluronic acid (HA) component comprising HA crosslinked with [BDDE]*

Kinney discloses a BDDE-crosslinked HA filler (Restylane) and a DEO-crosslinked HA filler (Puragen Plus). EX1012, 741-742. As discussed above, a POSITA would have been motivated to exchange the DEO crosslinker in Puragen Plus with a BDDE crosslinker. *See* EX1002 ¶¶ 182-185.

(iii) [1.1.2] *and uncrosslinked HA, wherein the HA component comprises greater than about 10% uncrosslinked HA by volume*

As explained in Grounds 1 and 2 (Section VI.B.2.a(iii)), crosslinked-HA fillers were known to incorporate uncrosslinked or "free" HA in varying amounts.

The POSITA would have been motivated to include uncrosslinked HA in the BDDE-double crosslinked filler and could have easily optimized the amount to obtain a desired extrusion force, including amounts greater than about 10% by volume. EX1002 ¶ 188.

(iv) [1.2] *lidocaine at a concentration of about 0.3% by weight*

"Puragen Plus contains … lidocaine HCl 0.3% …." EX1012, 742; *see also* EX1002 ¶ 182-183 (explaining this was a common concentration and effective to mitigate pain).

(v) [1.3] Process steps of claim 1 and claim 5

As discussed in Sections V.D and VI.B.2.a(v) (Ground 1 element [1.3]), the process steps of the claims are not entitled to patentable weight. Nevertheless, the claimed steps are also obvious in Ground 3.

Zhao teaches a process in which 0.1 gram of HA is dissolved in 1N NaOH and reacted with DEO to form ether crosslinks, followed by pH adjustment using 1N HCl with addition of additional DEO to form ester crosslinks. The crosslinked product was precipitated with anti-solvent, extracted several times with water, acetone, and isopropanol, and then dried at 37° C. to give the crosslinked product as a film. EX1058 ¶ [0090]. Zhao teaches the dried products may be swollen in a

PBS[16] formulation buffer to give a gel containing double crosslinked HA, NaCl, and phosphate buffer. EX1058 ¶ [0075]. *See also* EX1002 ¶ 186.

The POSITA could have easily adapted the above process using BDDE instead of DEO as the crosslinker to obtain a BDDE-double crosslinked gel. EX1002 ¶¶ 184-187. The POSITA, understanding that uncrosslinked HA could be used to optimize the injection characteristics of the gel, could have easily added a suitable amount of uncrosslinked HA to the gel. EX1002 ¶ 188.

As explained in Ground 1, Section VI.B.2.a(v)(c), there are a limited number of methods for combining lidocaine hydrochloride with a crosslinked gel. The POSITA would have been motivated to explore them all, including methods in which the pH of the double-BDDE-crosslinked gel was adjusted to a pH above about 7.5 prior to addition of lidocaine hydrochloride. The ’202 patent indicates that adding lidocaine HCl to a BDDE composition at pH 7.5 to 8 results in a final pH of about 7. Restylane is formulated at pH 7 (EX1006, 362); the skilled person would have been motivated to formulate the pre-sterilization double-BDDE-crosslinked filler at the same pH. EX1002 ¶ 189. If the POSITA was targeting a final pH of about 7 (such as was found in Restylane), routine optimization would

[16] PBS is a conventional abbreviation for Phosphate Buffer Saline. EX1002 ¶ 186.

necessarily lead to a pH adjustment to above about 7.5, as required by **claim 5**. EX1002 ¶ 190.

b. Independent claims 9, 17, and 25

As in Ground 1, the chart below indicates the parallel elements of claim 1 for independent claims 9, 17, and 25, and these claims are obvious in Ground 3 for the same reasons as claim 1.

Claims 9, 17, 25	
[9.pre] A stable, sterile soft tissue filler comprising: [17.pre] and [25.pre] *(identical)* A sterile, stable injectable soft tissue filler composition comprising:	See [1.pre] To the extent "injectable" in claims 17 and 25 is a limitation, Kinney discloses injectable fillers (EX1012, 741-742), and the POSITA would have used the modified filler in the same way. EX1002 ¶ 199.
[9.1.1] a hyaluronic acid (HA) component comprising HA crosslinked with [BDDE] [17.1.2] *and* [25.1.2] *(identical)* [a mixture of] crosslinked HA … being crosslinked with [BDDE]	See [1.1.1]
[9.1.2] and uncrosslinked HA; and [17.1.1] *and* [25.1.1] *(identical)* a mixture of soluble form hyaluronic acid (HA),	See [1.1.2]

Claims 9, 17, 25	
[9.2] lidocaine at a concentration of about 0.3% by weight of the soft tissue filler combined with the crosslinked HA component; [17.1.3] *and* [25.1.3] *(identical)* lidocaine in an amount effective to mitigate pain upon injection of the composition … [25.2] the lidocaine of the mixture being present in a concentration of about 0.3% by weight of the composition;	See [1.2]
[9.3] wherein the soft tissue filler is stable after heat sterilization at between about 120° C. and about 130° C.;	As discussed in Ground 1 above, a POSITA would have appreciated that the recited sterilization conditions were known to be effective to sterilize dermal fillers. Section VI.B.2.b(i). Further, Narins teaches heat-sterilization of Restylane in its final container. EX1007, 156. A POSITA would have been motivated to use this same technique for the double-BDDE-crosslinked composition. EX1002 ¶ 198. In doing so, the POSITA would have necessarily obtained a product that maintained its sterility (i.e., stability) until opened. EX1002 ¶ 199.
[9.4] wherein the soft tissue filler has a pH of about 7; and	Restylane is formulated at pH 7. EX1006, 362. A POSITA could have selected this pH for the double-crosslinked filler. EX1002 ¶ 195-196. Allergan

Claims 9, 17, 25	
	has not alleged or demonstrated any criticality or unexpected results associated with the claimed pH relative to any other physiologically appropriate pH.
[17.2] the composition having a HA concentration of between about 20 mg/ml and about 30 mg/ml;	Kinney discloses that multiple Restylane formulations "contain a concentration of 20 mg/mL" of HA and that "[e]ach milliliter of Puragen Plus contains 20 mg" of HA. EX1012, 741-742. The POSITA could have selected this concentration for the as-modified composition. EX1002 ¶ 203.
[9.5] wherein the stable, sterile soft tissue filler is made by a process comprising: [17.3] *and* [25.3] *(identical)* wherein the sterile, stable injectable soft tissue filler composition is made by a process comprising:	See [1.3]
[9.5.1] providing the HA component crosslinked with BDDE [17.3.1] *and* [25.3.1] *(identical)* providing the soluble form HA and crosslinked HA;	See [1.1.1]
[17.3.2] adjusting the pH of the soluble form HA and crosslinked HA; [25.3.2] adjusting the pH of the soluble form HA and crosslinked HA to an adjusted pH above about 7.2;	See [1.3]
[9.5.2] adding a solution containing lidocaine to the HA component crosslinked with BDDE to obtain a soft tissue filler; and	See [1.2], [1.3]

Claims 9, 17, 25	
[17.3.3] *and* [25.3.3] *(identical)* adding a solution containing lidocaine to the soluble form HA and crosslinked HA having the adjusted pH to obtain a HA-based injectable soft tissue filler composition; and	
[9.5.3] heat sterilizing the soft tissue filler to obtain a stable, sterile soft tissue filler. [17.3.4] *and* [25.3.4] *(identical)* heat sterilizing the HA-based injectable soft tissue filler composition to obtain the sterile, stable injectable soft tissue filler composition.	See [9.3]

c. Dependent claims 13, 21 and 27

As explained in Ground 1, claims 13, 21 and 27 recite the "adjusting" step adjusts the pH to "above about 7.5." This purported limitation is not patentable in Ground 3 for the same reason as discussed above for claim 5 (and element [1.3.2]).

d. Dependent claims 2-4, 10-12, 18-20, 26

Claims 2-3, 10-11, and 18-19 are obvious in Ground 3 for the same reason as shown in element [1.1.2] (and explained in Ground 1), namely that the recited ranges of uncrosslinked HA are obvious in view of Clark's teaching that Restylane has 25% soluble HA.

Claim 26 is obvious in Ground 4 for the same reasons described in Ground 2, namely that Smith suggests a POSITA could have selected any amount of uncrosslinked HA in the range of 10-20%.

Claims 4, 12, and 20 are obvious in Ground 3 for the same reason as shown in Ground 1, Section VI.B.2.d(ii): including 25% soluble HA (as in Restylane) in the hypothetical composition according to Kinney and Zhao would result in gel including particles of HA in a relatively fluidic medium of soluble HA. See EX1002 ¶ 193, 200, 204.

e. Dependent claims 6-8, 14-16, 22-24, 28-30

Ground 1 explained the features of these claims. While the recited process step (and its further limitations) is not entitled to patentable weight, Zhao nevertheless teaches the same process.

Zhao teaches the crosslinking reaction can occur at a pH greater than about 10, for instance at pH 10 to pH 12. EX1058 ¶ [0032]. Zhao exemplifies a process in which 0.1g HA is dissolved in 0.25N NaOH. EX1058 ¶ [0086]. While Zhao does not specify the physical form of the HA, nor whether it is protonated or in a salt form (e.g., NaHA), it does not matter because the resulting solution is the same in each case, an aqueous composition of NaHA at pH greater than about 10. EX1002 ¶ 194. Furthermore, Zhao teaches that HA is usually present as the sodium salt (EX1059 ¶ [0002]), and dry powders of the sodium salt were commercially available in 2008. EX1002 ¶ 194. The POSITA could have easily selected dry NaHA to use when preparing BDDE-double crosslinked HA.

D. Allergan cannot rebut the *prima facie* case of obviousness established above

As explained in Section IV.B, the Examiner allowed the claims of the challenged patent (and its related applications) based on Allergan's arguments and proffered evidence pointing to supposed "unexpected results" of the invention. But the inventor's three-page, unsubstantiated declaration is contradicted by the prior art cited above. Moreover, the 2012 Cui reference does not support Allergan's argument, which the Examiner apparently accepted, that Allergan's BDDE-crosslinked composition was "especially sensitive" to heat sterilization "relative to … non-BDDE crosslinkers." EX1023, 28. Finally, even if evidence of unexpected results was present (it is not), such evidence (or other secondary considerations) must be balanced against the other evidence of obviousness. *E.g.*, *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (holding claims obvious despite agreeing that results were unexpected). Allergan cannot rebut the *prima facie* case of obviousness presented in the Grounds here based on the arguments and evidence presented in prosecution.

1. The uncorroborated Inventor's Declaration does not accurately characterize the state of the art

As explained above, although Allergan did not formally submit the Lebreton declaration or Cui reference during the prosecution of the '202 patent, the Examiner clearly relied upon them when concluding that the claimed fillers were

unexpectedly stable. Allergan made several assertions, based on a § 1.132 Declaration from the inventor, regarding the POSITA's knowledge of the art and the expectations that would be drawn therefrom. Lebreton proffered several assessments of the state of the art, purportedly from the perspective of a POSITA "shortly prior to August 4, 2008":

> It was believed that adding lidocaine to [HA] gel compositions during manufacturing caused degradation of the [HA] prior to injection of the HA as a dermal filler.
>
> It was believed that lidocaine caused degradation of HA gel compositions during high temperature sterilization.
>
> It was not known whether HA compositions comprising lidocaine were stable or not after high temperature sterilization when placed in storage for any significant length of time.
>
> It was also believed that the instability of HA described above would have caused a viscosity reduction of the HA that would make it unsuitable for soft-tissue filling applications.

EX1024 ¶¶ 4-8. Lebreton's statements were *not* limited to BDDE-crosslinked HA, and Allergan's accompanying Response at the time included pending claims covering use of *any* crosslinker, not just BDDE. EX1023, 18-20 (claims 51-67). Allergan and the inventor cited *no* prior art to support the inventor's opinions. EX1024 ¶¶ 4-8 (repeatedly stating what "was believed"); *see also* EX1023, 24-28.

As shown here, contrary to Lebreton's statements, the totality of the prior art instead gave the POSITA the expectation lidocaine *could* be successfully combined with various crosslinked HA dermal fillers, including a BDDE-crosslinked HA dermal filler. *See* Sections III.C and Grounds, *supra*. The POSITA would have been aware of commercial lidocaine-containing crosslinked HA dermal fillers Elevess, Prevelle Silk and Puragen Plus, as well as the disclosures of the prior art documents cited here, including Sadozai, Kinney, and Reinmuller.[17] Each of these products and references explicitly state, or at minimum suggest, that crosslinked HA lidocaine-containing fillers were sterilized, and were sufficiently stable to be approved by FDA as a dermal filler. EX1002 ¶ 212.[18]

There is simply no evidence suggesting that a POSITA would have expected the addition of lidocaine would degrade crosslinked-HA compositions. See EX1002 ¶ 215 (Dr. DeVore unaware of any prior art suggesting issues with addition of lidocaine). In fact, a POSITA would have had the exact *opposite* expectation. Although Puragen Plus and Prevelle Silk are not explicitly described

[17] EX1059, 7:1-28.

[18] Abstracts of posters published in the February 2007 issue of the Journal of the American Academy of Dermatology also describe Anika's Elevess/CTA product (an embodiment of Sadozai) as "stable." EX1021, AB94 (P1039-P1040).

as sterile and stable, the POSITA would have known that these characteristics were necessary for FDA approval. EX1002 ¶ 217. And Sadozai and Kinney disclose that the lidocaine-containing crosslinked HA fillers had viscosities similar to, or even greater than, other crosslinked HA fillers that did not include lidocaine. EX1030 ¶ [0107]; EX1012, 746; Reinmuller discloses the heat sterilization of a lidocaine containing crosslinked HA filler, and that it was sufficiently stable to be stored and injected into a patient four times at intervals of 4 to 8 weeks. EX1059, 7:1-28. *See also* EX1021, AB94 (P1039 poster abstract teaching same). Each of these references supports the conclusion that the POSITA would have reasonably expected that lidocaine could be incorporated into a BDDE-crosslinked HA filler and heat sterilized without compromising the viscosity of the final product. *See* EX1002 ¶¶ 217-218. And rather than expecting lidocaine to *degrade* HA during autoclave sterilization, the prior art suggested that it could *increase* the stability. *See* EX1002 ¶ 218 (explaining teaching that lidocaine slowed the viscosity reduction process).

There is no evidence to support the inventor's characterization of the prior art. To the contrary, the evidence described herein clearly demonstrates that a POSITA would have reasonably expected that adding lidocaine to a crosslinked HA dermal filler—including the fillers disclosed by Lebreton—would result in a stable dermal filler. The Board should give the Lebreton declaration no weight. *See*

Velander v. Garner, 348 F.3d 1359, 1371 (Fed. Cir. 2003) (affirming Board's reliance on prior publications rather than "broad conclusory statements" … unsupported by corroborating references").

2. Example 4 does not provide evidence of non-obviousness

Lebreton also erroneously asserted the comparative data in the specification supported his conclusions. Although this Example does not appear in the '202 patent, it was included in each of the provisional applications, and the '202 patent incorporates them by reference. Lebreton declared that his experiments showed that the Samples 1-3 showed *more* of a decrease in viscosity after autoclave sterilization than Samples 4-5 (the allegedly inventive compositions). EX1024 ¶¶ 13-14. Lebreton declared that it was a "surprising and unexpected discovery" that the HA gels of his application "could be made to be heat and shelf stable." EX1024 ¶ 15. However, the cited evidence does not establish or suggest any meaningful differences between the claimed and the compared compositions.

For unexpected results to be probative of non-obviousness, the claimed subject matter must be compared with the closest prior art, and the difference must not have been expected by the POSITA at the time of the invention. *Kao Corp. v. Unilever U.S., Inc.* 441 F.3d 963, 970 (Fed. Cir. 2006). Moreover, the differences between the claimed invention and prior art must be significant and practical. *Cf. Galderma Labs., L.P. v. Tolmar, Inc.,* 737 F.3d 731, 739 (Fed. Cir. 2013)

("Unexpected results that are probative of non-obviousness are those that are 'different in kind and not merely in degree from the results of the prior art.' Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of [a POSITA]." (citations omitted). As explained below, the comparative examples in the provisional applications do not represent relevant prior art, nor do they represent a meaningful advance over prior art.

Even if Samples 1-3 experienced a more "substantial" drop in viscosity compared to Samples 4-6, as Allergan argued during prosecution, EX1023, 26, that alone would not make the resulting compositions unsuitable as dermal fillers. As explained by Dr. Devore, the reported viscosities of Samples 1-3 were all within an acceptable range to a POSITA. EX1002 ¶¶ 226-227; EX1039, 267. Further, the POSITA would have expected that the sterilized composition would not undergo any further viscosity reduction or other degradation. EX1002 ¶ 228.

Sample 2 is described in the provisional applications as the commercial product "Hylaform," an FDA-approved, DVS-crosslinked HA filler. EX1002 ¶ 229; EX1013, 26. The test results show that when pH of the pre-sterilization filler is 7.2, i.e., between about 7 and 7.4, the viscosity after autoclave remains within an acceptable range for use as a dermal filler. See EX1002 ¶ 229. As explained elsewhere in this petition, the POSITA would have known that prior to sterilization,

the pH of the filler should be brought to this range. *See* Sections VI.B.2.a(v)(c); VI.C.2.a(v), EX1002 ¶¶ 98, 172), Thus, there is nothing in Example 4 suggesting that Hylaform could not be combined with lidocaine.

The test results and samples do not support patentability or the claimed unexpected results for other reasons as well. For instance, Dr. DeVore explains that the patent's experiments on Sample 1 were irrelevant because he was not aware of such a composition being used as a dermal filler, either in 2008 or now. EX1002 ¶ 225.

As for Sample 3,[19] Allergan argued during prosecution that it lost viscosity to autoclave sterilization. EX1023, 24-28. The data actually shows the opposite and supports that Sample 3 is not indicative of unexpected results. Figure 3 shows that when the pre-sterilization Sample 3 is between 7 and 7.4, the resulting composition's viscosity *increases* relative to the non-lidocaine sample after autoclave stabilization by about 10%. See EX1002 ¶ 230; U.S. Patent 8,357,795, Figure 3; EX1013, 39 (Figure 4).

[19] The provisional applications describe this sample as "believed to be similar" to Restylane. EX1013, 26.

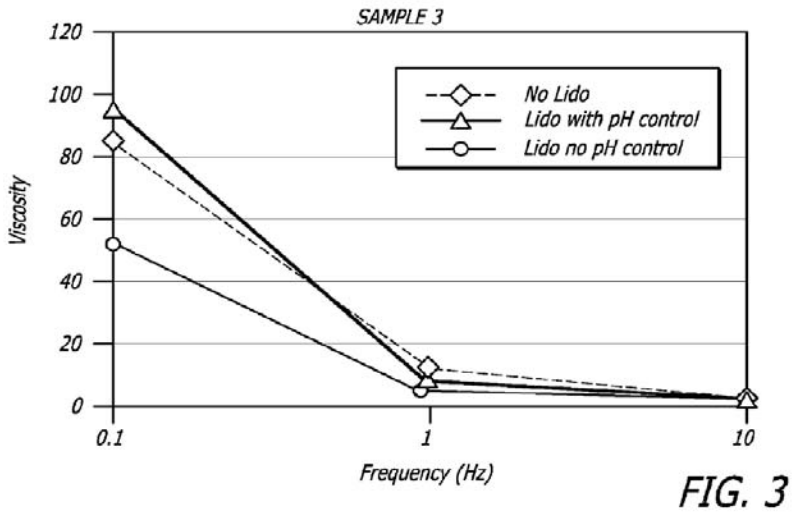


FIG. 3

Allergan acknowledges this fact in the specification of the provisional application: Sample 3 (a non-cohesive BDDE-crosslinked HA composition) gave the same results as Samples 4 and 5 (cohesive BDDE-crosslinked HA compositions). EX1002 ¶ 35; EX1013, 27. Moreover, it is irrelevant that the pre-sterilization Samples that had lower pH values exhibited lower viscosities. A POSITA would have understood that a filler should be formulated at a physiologically acceptable pH (for instance 7 or 7.2 in the Grounds here, or 7.0 to 7.4 more generally). EX1002 ¶¶ 98, 230. Therefore, examples where compositions were sterilized at *lower* pH values would not have affected a POSITA's expectation that lidocaine could be incorporated in a crosslinked HA dermal filler.

Finally, Allergan also argued that Sample 3 (when sterilized at a pH lower than 7.2) underwent a 35% reduction in viscosity, whereas Sample 4 (when sterilized at a pH lower than 7.2) exhibited a 30% reduction of viscosity. EX1023,

26-27. As explained by Dr. Devore, these data are irrelevant because such a small difference is meaningless, and a single experiment is not statistically significant. EX1002 ¶¶ 231-232.[20]

3. Cui is not relevant

The last piece of "evidence" Allergan relied upon to show "unexpected results" was the Cui reference (EX1025). Allergan argued that Cui "shows" that BDDE-crosslinked HA fillers were "known to be especially sensitive to heat sterilization relative to HA crosslinked with other, i.e. non-BDDE, crosslinkers," so that "the discovery" of Allergan's sterile compositions was "surprising," given the supposedly unstable nature of HA-based gels crosslinked with BDDE even without the addition of lidocaine. EX1023, 28.

Cui compares the stability of BDDE-crosslinked HA with HA crosslinked with three other crosslinking agents. EX1025, 1506. But Cui does *not* test or compare BDDE to *any* of the three crosslinking agents that were known in the art and approved by FDA or undergoing U.S. clinical trials in August 2008. *Compare*

[20] Allergan has not provided any argument or evidence explaining why such a small difference is meaningful to a POSITA. *See Galderma*, 737 F.3d at 739.

id., with Section III.B; EX1002 ¶ 221.[21] Moreover, none of the crosslinkers appear to have even been used as dermal fillers as of the application's filing date. EX1002 ¶ 221.

Moreover, Cui was published in 2012, well after the claimed priority date of the patent. The reasonable expectation of success is evaluated at the time the invention was made—a later published reference that might have taught away from the claimed invention is irrelevant. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.* 752 F.3d 967, 976 (Fed. Cir. 2014) ("Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art *at the time of invention*." (quoting *Velander v. Garner*, 348 F.3d 1359, 1377 (Fed. Cir. 2003)); *id.* at 977 ("[E]vidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention."). Cui could not have informed the POSITA's expectation of BDDE-crosslinked HA stability *at the time the application was filed*, because Cui did not publish until years later.

[21] Cui also does not evaluate the effect of lidocaine on any of the compositions it tested. *See generally* EX1025.

Thus, Cui is irrelevant to the question of whether Allergan's BDDE-crosslinked HA composition showed unexpected results compared to the other crosslinkers known to POSITAs at the time. EX1002 ¶ 222. Cui is not prior art; but even if it was, Cui is plainly not the "closest prior art" that would be relevant to the obviousness and unexpected results analysis. *Kao Corp.*, 441 F.3d at 970.

4. Other Secondary Considerations

Prollenium is not aware of any other secondary considerations that are sufficient to rebut the *prima facie* case of obviousness presented in the Grounds above.[22] To the extent Allergan should raise secondary indicia such as commercial success, industry praise, or long-felt need, in its Preliminary Response, the Board should institute trial so the parties may develop the evidence before the Board considers the merits of any such argument. *See*, *Celltrion, Inc. v. Genetech, Inc.*, IPR2017-01374, Paper 15, 17-18 (Dec. 1, 2017) (instituting trial to permit parties to develop a record regarding secondary considerations first raised in Preliminary Response).

[22] There have been no final determinations regarding secondary indicia in any of the litigations involving the Allergan patents.

5. Summary

In sum, the evidence cited in this Petition, including both documents and testimony by Dr. DeVore, refute the alleged unexpected results advanced by Allergan during prosecution. In light of the many disclosures of sterilized, non-BDDE-crosslinked HA fillers known to a POSITA at the time, Allergan's "unexpected results" evidence does not hold water; it certainly does not show the claims to be nonobvious. All the evidence cited by Allergan is either incorrect or irrelevant.

The Examiner relied on Allergan's "unexpected results" arguments to allow the claims—in this patent and across its entire family. *See, e.g.*, EX1023, 8-9; EX1033, 8; EX1040, 8; EX1089, 4 (notices of allowance). As shown here, the claims are unpatentable in view of the evidence and the lack of support for Allergan's claim of unexpected results. Finally, these apparent contradictions between the "evidence" that persuaded the Examiner to allow the claims and the new evidence and argument in this Petition are also important to the Board's analysis under § 325(d), as described in the following section. This Petition asks the Board to remedy the Examiner's error, which has propagated throughout an entire family—including applications still pending at the Office.

VII. DISCRETIONARY FACTORS FAVOR INSTITUTION

The factors considered under 35 U.S.C. §§ 314(a) and 325(d) do not weigh in favor of exercising discretion to deny institution. As an initial matter, this is the first Petition challenging this patent. So the *General Plastic* factors and analysis do not apply here. *Cf. Prollenium v. Allergan*, IPR2019-01519, Paper 17, 43-46 (Mar. 19, 2020) (instituting trial, agreeing *General Plastic* does not apply but still finding factors favor Prollenium).

A. Section 325(d) factors

The Board considers several factors to evaluate whether to exercise its discretion under § 325(d). *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 Paper 6, 9-11 (Feb. 13, 2020) (precedential). The Board should not decline to institute trial because even though *one* of the same prior art references was cited by the Office during prosecution, the Grounds here present new evidence and arguments that show how the Office materially erred by relying on the Lebreton Declaration to overcome the rejection.

All references cited in the Grounds except for Zhao appear on the face of the ’202 patent, but the grounds here provide a much more compelling argument for obviousness that was ever assembled by the Office. The Office relied on Lebreton

as a primary reference in the ancestor '768 application (and related '884 application), citing Wang and Calias (EX1047, EX1048, respectively) for a motivation to add lidocaine. Allergan overcame Calias rejection by arguing a POSITA would have expected that the addition of lidocaine would unacceptably reduce the composition's viscosity. EX1023, 23. However, Wang and Calias merely *suggest* that lidocaine *could* be added to a HA composition, and do not refute Allergan's position that lidocaine was expected to degrade the filler upon sterilization.

Here, Kinney and Sadozai cited in the Grounds—as well as CTA Summary, Reinmuller, Toth, and Hanke cited as supporting evidence of the knowledge and skill of a POSITA—all disclose a working embodiment of lidocaine successfully combined with a crosslinked HA composition. The Office plainly overlooked the relevance of each of these references when crediting the inventor's declaration as evidence of obviousness. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 10-11. Allergan never rebutted the Office's prima facie conclusions that the claims were obvious over the prior art; it did not even challenge the Office's assertion that Lebreton taught most of the elements of the claims. Rather, the ancestor patents and the challenged patent were allowed based on Allergan's proffered unexpected results and declaration concerning the supposed state of the art and knowledge of the POSITA. The prior art (and DeVore testimony) cited here contradict the

unsupported inventor declaration relied on by the Office. Thus, the Office materially erred in relying on the Lebreton Declaration to overcome the prior art.[23]

The asserted grounds here also provide a completely new § 103 analysis based on Kinney and Zhao that was not considered by the Examiner. While the Examiner contended that it would have been obvious to modify the Lebreton reference by adding lidocaine, he apparently did not consider that it would have been equally obvious to modify the crosslinker in the lidocaine-containing filler taught by Kinney, or that Zhao would have enabled the POSITA to do so.

The Board should not exercise its discretion because the substantial evidence cited in this Petition shows the Examiner had an incomplete understanding of the prior art and, consequently, he erred in accepting the applicant's unsubstantiated declaration attesting to "unexpected results." Moreover, this Petition provides evidence showing the inventor's representations about the state of the art at the priority date were incorrect, and the Examiner erred in relying on those

[23] The Board reached the same conclusion in declining to exercise its discretion to deny institution in seven proceedings challenging six related patents to this one, relying on the same prior art as the current petition. *E.g.*, IPR2019-01505, Paper 18, 35-42 (Mar. 19, 2020) (finding *Becton Dickinson* factors favored Petitioner and instituting trial).

representations. Even if the inventor's declaration had accurately characterized the state of the art (it did not), this petition also provides new evidence, not considered by the Office during prosecution, identifying flaws in both the design and interpretation of the comparative experiments. *See* Section VI.D.2. And as explained in Section VI.D and Dr. DeVore's declaration, the Office erred to the extent it relied on Cui as evidence of non-obviousness. Accordingly, the Board should not exercise its discretion under § 325(d) to deny institution.

VIII. CONCLUSION

Challenged claims 1-30 are unpatentable, and Petitioner respectfully requests that the Board institute trial.

IX. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Parties in Interest

The real parties-in-interest are Prollenium US Inc. and Prollenium Medical Technologies Inc.

B. Related Matters

Allergan has asserted the challenged patent and U.S. 10,485,896 (the '896 patent) against Petitioner Prollenium in *Allergan USA, Inc. et al v. Prollenium US Inc. et al.*, Case-No. 1:20-cv-00104-CFC (D. Del. filed Jan. 23, 2020) ("the 2020 litigation"). Allergan has also asserted six other patents related to the challenged

patent in *Allergan USA, Inc. et al v. Prollenium US Inc., et al.*, Case No. 1:19-cv-00126 (D. Del. filed Jan. 22, 2019) ("the 2019 litigation").

Prollenium has filed petitions challenging all patents asserted in the 2019 litigation:

- On August 23, 2019, Prollenium filed a petition in IPR2019-01508 challenging related U.S. Patent No. 9,238,013. Trial was instituted on March 19, 2020.
- On September 3, 2019, Prollenium filed petitions IPR2019-01505 and IPR2019-01509 challenging related U.S. Patent Nos. 8,450,475 and 9,358,322, respectively. Trial was instituted on both patents on March 19, 2020.
- On September 16, 2019, Prollenium filed a petition in IPR2019-01617 challenging related U.S. Patent No. 8,822,676. Trial was instituted on March 20, 2020.
- On September 20, 2019, Prollenium filed two petitions, IPR2019-01506 and IPR2019-01632, challenging related U.S. Patent No. 8,357,795. Trial was instituted for both petitions on March 31, 2020.
- On October 25, 2019, Prollenium filed a petition in IPR2020-00084 challenging related U.S. Patent 9,089,519. Trial was instituted on April 10, 2020.

Allergan filed the follow-on, 2020 litigation about three months after the *last* of Prollenium's petitions challenging the patents from the 2019 litigation, after most of Allergan's Preliminary Responses were filed in the first set of IPRs, and

even after Prollenium filed its consolidated Reply to Allergan's Preliminary Responses.

On May 20, 2020, the district court granted Prollenium's motion to stay the 2019 litigation pending the outcome of the IPRs listed above. Prollenium is also concurrently filing a petition challenging the '896 patent in proceeding IPR2020-00901. No Scheduling Order has been entered and no trial date has been set in the 2020 litigation as of the filing of this Petition. The parties have conferred with the court about staying the 2020 litigation pending the resolution of this IPR and the IPR on the '896 patent, and Prollenium will be filing a motion to stay the 2020 litigation.

Prollenium believes that it would be most efficient to assign all these petitions to the same panel reviewing the other members of Allergan's patent family. Allergan has multiple issued patents and pending continuations applications claiming priority to one or more of these patents as well.

C. Lead and Back-Up Counsel and Service Information

Petitioner identifies the following counsel for this proceeding:

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Petitioner consents to electronic service by email to:

mcc.prollenium.ipr@mcciplaw.com.

Respectfully submitted,

/Christopher L. Curfman/
Christopher L. Curfman (Reg. No. 52,787)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on June 2, 2020, a copy of this Petition and all exhibits were served on the counsel of record for the Patent Owner by shipping via FedEx Overnight shipping:

Morgan, Lewis & Bockius LLP
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Costa Mesa, CA 92626-7653

An electronic copy of the petition and accompanying exhibits has also been served via email on the following counsel representing the Patent Owner in related district court litigation pending IPR proceedings:

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), Petitioner certifies that the foregoing Petition for *Inter Partes* Review contains 13,771 words, excluding the portions as permitted by § 42.24(a).

/Christopher L. Curfman/
Christopher L. Curfman (Reg. No. 52,787)